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Archives OF NEUROLOGY AND PSYCHIATRY

MARCH 1955

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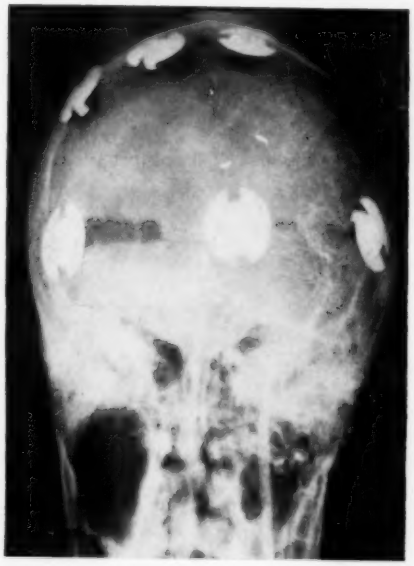

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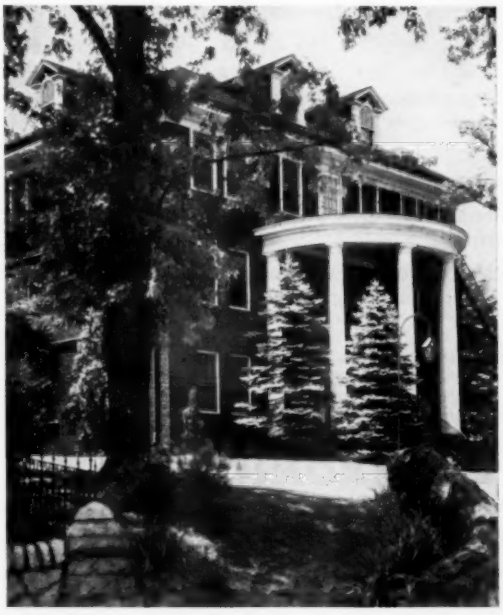

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Cerebrospinal Fluid Inorganic Phosphorus in Acute Poliomyelitis

Study of One Hundred Four Patients

LOUIS ODESSKY, M.D., New York
PHILIP ROSENBLATT, M.D.
IRVING J. SANDS, M.D.
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Phosphorus, in the form of phosphate, is one of the largest and most important constituents of central nervous system tissue, and therefore its determination in cerebrospinal fluid, which has been made rarely in poliomyelitis, might provide information on the diagnosis, course, and treatment of the disease. During the 1952 epidemic of poliomyelitis inorganic phosphorus levels in 110 cerebrospinal fluids were determined on 104 patients during the acute phase, and this report evaluates the findings. There was a previous report of cerebrospinal fluid inorganic phosphorus in four poliomyelitis patients by Wilcox, Lyttle, and Hearn [1] in 1925.

Presented at the Clinical Pathological Conference, Oct. 1, 1953, the Kingston Avenue Hospital.

From the Communicable Disease and Laboratory Services of the Kingston Avenue Hospital, 600 Albany Ave., Brooklyn.

Presented, in part, at the 78th Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 14-16, 1954.

Present Address: Department of Pathology, Goldwater Memorial Hospital, Welfare Island, New York 17 (Dr. Odessky).

MATERIAL AND METHODS

Patient Material.—During the 1952 poliomyelitis epidemic, 255 patients were hospitalized with poliomyelitis in the Kingston Avenue Hospital, the communicable diseases hospital for the nearly 3,000,000 people of the borough of Brooklyn. From the time (July 9, 1952) that determinations of cerebrospinal fluid inorganic phosphorus levels were started in poliomyelitis patients, 235 patients were seen at our hospital. In 104 of these patients inorganic phosphorus in the cerebrospinal fluid was determined; in the others inorganic phosphorus was not determined because (*a*) not enough fluid was available for the determination, (*b*) the patients had been first seen at other hospitals, where the diagnostic spinal puncture had been performed, and (*c*) in a few instances spinal puncture was not done because the patients had to be put into a respirator immediately on arrival at our hospital. However, every inorganic phosphorus level determined in the cerebrospinal fluids from patients with poliomyelitis has been included in this report.

All specimens were obtained during the acute phase of the illness on the day of, or the day after, admission except for eight values, which were determined 2, 3, 3, 5, 9, 11, and 13 days, and 3 weeks, respectively, after admission.

Method.—Cerebrospinal fluid inorganic phosphorus was determined by a modified Fiske and SubbaRow procedure (Odessky, Rosenblatt, Bedo, and Landau [2]).

Cell counts, total protein, globulin, and sugar were determined on all fluids. Also, direct smears and cultures were made on every fluid.

RESULTS

The data on inorganic phosphorus from 110 cerebrospinal fluids on 104 patients in the acute stage of poliomyelitis are presented in Table 1. Also included are the data on four fluids without inorganic phosphorus determinations from four patients who had spinal punctures performed twice but on whom inorganic phosphorus was determined on only one occasion.

TABLE 1.—*Cerebrospinal Fluid Data in Acute Poliomyelitis*

Case No.	Sex	Age, Yr.	Inorganic Phosphorus, Mg. per 100 Ml.	Cells per Cu. Mm.	Total Protein, Mg. per 100 Ml.	Globulin	Sugar, Mg. per 100 Ml.	Condition at Time of Discharge*
1	M	1	1.9	60	44	Very faint trace	75	++
2	F	3	1.7	169	75	Faint trace	71	++
3	F	3	2.1	64	48	Faint trace	76	+++
4	M	3	2.1	20	30	Negative	71	0
5	F	3	1.6	127	38	Negative	90	+
6	F	3	1.9	112	46	Very faint trace	71	++
7	M	3	1.5	50	38	Negative	74	++
8	F	3	2.4	49	56	Very faint trace	67	++
9	M	3	2.0	28	47	Negative	66	++
10	M	3	2.7	85	65	Negative	80	++
11	M	4	1.5	140	25	Negative	87	++
12	F	4	1.6	178	90	Faint trace	94	++
13	M	4	1.9	18	25	Negative	74	+
14	F	4	1.4	801	65	Trace	70	++
15	M	4	1.8	38	21	Negative	79	0
16	F	4	1.8	226	103	Heavy	69	+++
17	M	4	1.9	34	26	Negative	74	+
18	M	4	1.5	30	30	Negative	77	++
			2.1	0	24	Negative	91	(11 days later)
			2.0	0	22	Negative	81	(3 wk. later)
19	M	5	2.2	3	24	Negative	84	0
20	F	5	1.9	6	21	Negative	80	0
			2.0	2	20	Negative	83	(13 days later)
21	M	5	1.9	34	54	Very faint trace	81	+
22	M	5	1.5	274	38	Negative	64	0
23	M	5	1.4	506	43	Faint trace	70	0
24	F	5	1.6	480	68	Very faint trace	83	+++
25	M	5	...	1060	87	Trace	61	0
			1.7	157	53	Faint trace	73	(2 days later)
26	M	5	1.9	..	45	Faint trace	86	+
27	M	5	1.7	65	41	Very faint trace	88	0
28	M	5	2.0	80	53	Negative	68	0
29	F	5	2.0	350	64	Very faint trace	83	++
30	M	5	1.1	1000+	48	Very faint trace	63	0
31	M	5	2.0	4	26	Negative	..	0
32	F	5	1.7	167	62	Trace	83	++
33	F	6	1.3	66	60	Faint trace	68	+
34	M	6	1.7	28	28	Negative	72	0
35	F	6	2.7	236	70	Faint trace	66	0
36	F	6	2.4	150	58	Faint trace	77	+
37	M	6	1.4	180	75	Faint trace	78	+
38	M	7	1.7	30	31	Negative	72	0
39	M	7	1.8	200	62	Faint trace	77	+
40	M	7	2.0	576	103	Trace	63	0
41	F	7	2.2	20	60	Faint trace	72	++
42	M	7	1.9	150	76	Faint trace	88	++
43	F	7	2.1	593	68	Faint trace	76	0
			2.3	114	34	Negative	68	(9 days later)
44	F	7	1.4	21	37	Negative	85	0
45	M	7	1.5	246	48	Faint trace	88	0
46	F	7	2.1	102	36	Very faint trace	76	0
47	F	8	2.0	38	27	Negative	73	+
48	M	8	2.1	137	41	Very faint trace	80	0
49	M	8	2.2	48	48	Negative	75	0
50	M	8	1.6	3	32	Negative	77	+
51	M	8	1.8	300	29	Negative	76	+
52	M	8	2.1	0	24	Negative	70	0
53	M	9	3.1	898	71	Trace	79	+
54	M	9	1.8	120	53	Very faint trace	69	0
55	M	9	1.4	63	83	Faint trace	83	+
56	F	9	1.8	90	33	Negative	72	++
57	M	9	1.4	121	55	Faint trace	96	+
58	M	9	1.9	600	81	Faint trace	76	Died 4 days later
59	M	9	2.0	0	23	Negative	79	0
60	F	10	2.0	245	41	Very faint trace	69	++
61	F	11	2.4	2	82	Faint trace	82	++
62	F	11	1.9	45	95	Faint trace	83	+++

TABLE 1.—*Cerebrospinal Fluid Data in Acute Poliomyelitis*—Continued

Case No.	Sex	Age, Yr.	Inorganic Phosphorus, Mg. per 100 Ml.	Cells per Cu. Mm.	Total Protein, Mg. per 100 Ml.	Globulin	Sugar, Mg. per 100 Ml.	Condition at Time of Discharge*
63	M	11	2.3	0	31	Negative	82	0
64	M	11	2.3	120	108	Trace	80	Died 6 days later
65	F	12	2.5	710	153	Trace	67	++
66	M	12	...	500	72	Faint trace	74	+
			1.4	82	48	Very faint trace	74	(5 days later)
67	M	12	1.5	..	91	Trace	83	+++
68	F	12	2.1	560	100	Faint trace	68	0
69	F	13	2.1	44	48	Very faint trace	70	0
70	M	13	1.5	250	67	Faint trace	72	0
71	M	13	2.1	14	29	Negative	81	0
72	M	14	2.6	6	37	Negative	83	0
73	F	14	2.5	2	21	Negative	74	0
74	M	14	2.2	100	36	Very faint trace	86	0
75	M	14	1.6	135	118	Heavy	85	+++
76	M	16	...	64	86	Faint trace	..	++
			1.7	104	61	Faint trace	67	(1 day later)
77	M	16	2.2	27	111	Faint trace	68	++
78	F	17	1.7	4	58	Negative	75	0
79	M	17	1.4	80	68	Very faint trace	74	+++
80	M	18	1.5	92	66	Faint trace	65	+
81	M	18	1.8	352	130	Heavy	70	+++
82	M	19	1.6	216	56	Very faint trace	63	0
83	F	19	1.5	318	54	Faint trace	79	+++
84	F	20	2.0	176	81	Faint trace	97	Died 10 hr. later
85	F	20	1.3	310	124	Faint trace	63	0
86	F	21	1.5	100	49	Very faint trace	67	0
87	F	21	2.2	12	53	Very faint trace	65	++
88	M	22	2.0	260	95	Trace	68	0
89	F	22	1.7	75	36	Very faint trace	66	0
90	M	22	1.4	268	65	Faint trace	80	+++
91	M	22	1.5	28	92	Faint trace	98	+++
			1.5	0	38	Negative	91	(3 days later)
92	F	23	1.8	184	97	Faint trace	88	+++
93	M	23	2.0	36	47	Negative	81	Died 2 days later
94	M	23	1.6	120	53	Trace	65	0
95	M	24	1.5	15	38	Negative	71	0
96	F	24	1.8	64	56	Very faint trace	82	0
97	M	24	2.1	333	46	Very faint trace	88	+++
98	F	25	1.5	256	98	Trace	64	++
99	F	26	2.3	0	26	Negative	75	0
			...	1	56	Very faint trace	66	(4 days later)
100	M	29	2.0	330	..	.....	93	Died 18 hr. later
101	F	31	1.6	20	125	Trace	75	Died 7 days later
102	M	33	2.1	150	54	Faint trace	76	++
103	M	30	2.3	0	57	Very faint trace	62	+
			2.6	113	79	Faint trace	73	(3 days later)
104	F	47	2.2	80	133	Faint trace	70	++

* 0 indicates patients who were discharged home without any apparent residuals. The *admitting* signs and symptoms in this group of 42 patients were distributed as follows: nuchal rigidity, 29; spinal rigidity, 11; slight to marked muscle weakness, 5 (Cases 4, 25, 38, 44, and 59); pain, 7; positive Kernig sign, 13; positive Brudzinski sign, 14; diminished deep tendon reflexes, 3; absent deep tendon reflexes, 3; increased knee jerk, 1; clonus, 1; positive Babinski sign, 1; bulbar paralysis, 3 (Cases 20, 44, and 45); headache, 10; drowsiness, 2; encephalitis in addition to spinal symptoms, 1 (Case 94). + indicates patients who were discharged home with minor residuals; ++, patients who were discharged to an orthopedic hospital with moderate residuals; +++, patients who were discharged to an orthopedic hospital with severe residuals, almost complete paralysis of one or more extremities or a major group of muscles.

The cerebrospinal fluid inorganic phosphorus levels ranged from 1.1 to 3.1 mg. per 100 ml. The mean inorganic phosphorus value is 1.9 mg. per 100 ml., with a standard deviation of ±0.36 mg. per 100 ml. and a standard error of the mean of ±0.03 mg. per 100 ml. The difference between the mean of cerebrospinal fluid inorganic phosphorus of these poliomyelitis patients, 1.9 mg. per 100 ml., and that of our control patients,[2] 1.4 mg. per 100 ml., is 5.5 times the sum of the two respective standard errors of the mean, indicating that the data are highly significant. The mean value for cerebrospinal fluid inorganic phosphorus of our poliomyelitis patients is increased 36% over that for our

control patients. Forty-eight values (44%) of 2.0 mg. per 100 ml., or more, were definitely elevated, while 62 values (56%) of 1.9 mg. per 100 ml., or less, ranged from the upper limit of normal to normal levels.

Ninety-one cerebrospinal fluids (83%) had counts of 10 or more cells per cubic millimeter; of these, lymphocytes predominated or equaled polymorphonuclear leucocytes in approximately 70% of the specimens, polymorphonuclear leucocytes predominating in the others. The total protein values ranged from 20 to 153 mg. per 100 ml.; 68 cerebrospinal fluids (62%) had a total protein in excess of 45 mg. per 100 ml. Seventy-one cerebrospinal fluids (65%) gave a positive reaction for globulin. The sugar values ranged from 61 to 98 mg. per 100 ml.; 75 sugar levels were between 61 and 80 mg. per 100 ml.; 27, between 81 and 90 mg. per 100 ml., and 7, between 91 and 98 mg. per 100 ml.

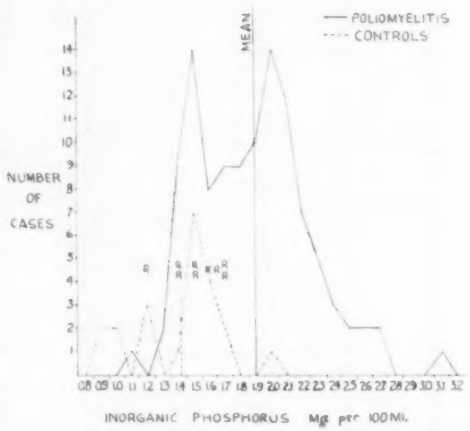
All direct smears were negative, and all cultures proved sterile.

A comparison of elevated inorganic phosphorus and other findings disclosed that of those 48 cerebrospinal fluids having inorganic phosphorus levels of 2.0 mg. per 100 ml. or higher, 35 had pleocytosis, 28 had total protein in excess of 45 mg. per 100 ml., and 27 had a positive reaction for globulin. There is a suggestion that the increase in cerebrospinal fluid inorganic phosphorus appears as a later manifestation of the disease, since the relative number of elevated values above the mean value of 1.9 mg. per 100 ml. increased as the cytology of the cerebrospinal fluid changed from polymorphonuclear leucocytes to lymphocytes. In the cerebrospinal fluids in which the inorganic phosphorus values were 2.0 mg. per 100 ml., or more, polymorphonuclear leucocytes predominated in 11%; the number of polymorphonuclear leucocytes and lymphocytes were approximately equal in 19%, and lymphocytes predominated in 70%, while in the cerebrospinal fluids in which the inorganic phosphorus values were 1.9 mg. per 100 ml., or less, polymorphonuclear leucocytes predominated in 32%, the number of polymorphonuclear leucocytes and lymphocytes were approximately equal in 22%, and lymphocytes predominated in 46%.

There was no correlation between the inorganic phosphorus values and the ages of the patients.

COMMENT

Our results indicate that cerebrospinal fluid inorganic phosphorus is elevated in acute poliomyelitis. This is illustrated graphically in the accompanying Figure, in which



Frequency distribution of 110 cerebrospinal fluid inorganic phosphorus values from 104 patients with typical average acute poliomyelitis (straight line), as against our control patients [2] (broken line). The vertical lines indicate the mean cerebrospinal fluid inorganic phosphorus values, 1.9 and 1.4 mg. per 100 ml., for the respective curves. *R* signifies a mean value for "normal" cerebrospinal fluid inorganic phosphorus as reported by investigators in the literature, 1.2,[3] 1.4,[4] 1.4,[5] 1.5,[6] 1.5,[7] 1.6,[8] 1.7,[1] 1.7,[9] and 1.7 [10] mg. per 100 ml. Note that the poliomyelitic curve is shifted to the right, toward the elevated, abnormal values, when compared with our control patients [2] or with the mean values of normals reported by others (*R*).

it is seen that the distribution of inorganic phosphorus levels in acute poliomyelitis (solid line) is shifted to the higher abnormal values when compared with our control patients (broken line) or with the mean values reported by other investigators: 1.2,[3] 1.4,[4] 1.4,[5] 1.5,[6] 1.5,[7] 1.6,[8] 1.7,[1] 1.7,[9] and 1.7 [10] mg. per 100 ml., all represented by the letter *R* on the graph.

These results are valid only if the distribution of our patients is a random one. To

ascertain randomness, we compared the distribution of our patients with regard to outcome of residuals with the figures given by the National Foundation for Infantile Paralysis.[11] Of our 104 patients (last column of Table 1), 58% recovered completely or remained with minor residuals; 24% remained with slight to moderate muscle weakness; 12% were disabled, and 6% were fatalities. The National Foundation for Infantile Paralysis states that of every 100 patients, about 50% will recover completely; 30% will have slight muscle weakness; 12% will be disabled, and 8 may die.[11] Thus, our 104 patients fall into a random distribution pattern compatible with the general trend of residuals and fatalities of poliomyelitis patients. The age distribution of our series was similar to that reported for New York City and State or nearby states * except for the 20-year and over-age group, which constituted a slightly higher proportion of our cases (20%; Table 1) than that generally observed for 1946 or previous years (15%, or less.)* Furthermore, the sex ratio of our 104 patients is 61 males to 39 females. This is in accord with the consistent findings of other investigators, who noted a slightly higher incidence of males over females, 56:44, in 24,766 reported cases of poliomyelitis.† The ratio varied from that similar to ours, 60:40 (Fischer and Stillerman [16] and Grulee Jr. and Panos [24]) to 53:47. Thus, our series of poliomyelitis patients (Table 1) is representative of average poliomyelitis.

Determinations of inorganic phosphorus in cerebrospinal fluid in acute poliomyelitis apparently have seldom been made. In 1925 Wilcox, Lyttle, and Hearn [1] reported cerebrospinal fluid inorganic phosphorus values in four poliomyelitis patients. They found 2.0 mg. per 100 ml. in a 2-year-old child on the third day of the disease and 2.1, 1.8, and 2.0 mg., per 100 ml. in a 3½-year-old child on the 6th, 11th, and 18th days of the infection, respectively. In a 9-year-old child with abortive poliomyelitis the value for cerebrospinal fluid inorganic phosphorus was 1.6 mg. per 100 ml. on the 10th day of the disease, and in a 2½-year-old child who had had poliomyelitis sometime previously the level was 1.9 mg. per 100 ml. The values in the acute stage, those of the first two patients, are in accord with the results that we obtained.

It has been established that serum inorganic phosphorus levels decrease with increasing age, but data available on inorganic phosphorus values from true "normal" cerebrospinal fluids at the present time are insufficient to permit one to state that this is true also for the cerebrospinal fluid. The cerebrospinal fluids from our patients with acute poliomyelitis showed no correlation between age and the values found for inorganic phosphorus.

An attempt was made to relate the cerebrospinal fluid inorganic phosphorus values with the date of onset of the disease. However, in most instances, this could only be approximated; hence, this attempt was abandoned.

Pleocytosis of the cerebrospinal fluid still seems to be the best initial index of central nervous system involvement in poliomyelitis —although, of course, it is no more indicative, in and of itself, of a diagnosis of poliomyelitis than is the increase in cerebrospinal fluid inorganic phosphorus level—because of all diagnostic determinations, the cerebrospinal fluid cell count appears to be the first to become pathognomonic. However, because the cerebrospinal fluid cell count drops to normal rapidly, in most cases by the end of the first week, and in many other cases even within a day or two of onset, the finding of a normal cell count cannot necessarily rule out the diagnosis of poliomyelitis. Nicholls [29] stressed that the day of the disease when the spinal tap is done is one of the most important factors to be taken into consideration in evaluating the cerebrospinal fluid findings. She also reported [30] on the follow-up studies of poliomyelitis patients with normal cerebrospinal fluid cell counts and normal values for total protein: Of 43 such patients, 51% had recovered completely, 35% had residual weakness, and 14% remained with severe

* References 12 to 15.

† References 16 through 28.

paralysis. Ytrehus,[31] similarly, found six patients with poliomyelitis who had a normal cerebrospinal fluid at the time of admission. Five patients with poliomyelitis who revealed normal cerebrospinal fluid cell counts but positive reactions for globulin were reported by Levinson,[32] who reviewed similar instances in the literature. The cell count itself follows a pattern, normal at first, then a rise to a peak and a decline to normal; therefore, it varies, depending upon the point on this curve that the cerebrospinal fluid is obtained. The rapidity with which the degree of pleocytosis is altered is exemplified in our series in Table 1 by Case 25, which had a cell count of 1,060 per cubic millimeter at the time of the first spinal puncture; less than two days later the cell count of the cerebrospinal fluid was 157 per cubic millimeter, a drop of 85% in a very short time! Thus, pleocytosis is not an infallible guide in diagnosing poliomyelitis. In our patients (Table 1) there were 11 fluids (11%) which had counts of 500, or more, cells per cubic millimeter, making a diagnosis of an infection other than poliomyelitis an important consideration in the initial therapy of the patient. In poliomyelitis the increase in inorganic phosphorus, with a trend to higher levels as the cytology shifts from polymorphonuclear leucocytes to lymphocytes, or in total protein appears to take place after the rise in cells, suggesting to early workers that the determination of cerebrospinal fluid protein levels be used as a means of detecting nonparalytic poliomyelitis (Andelman and associates[33]). Therefore, it is not at all unusual to find a normal cerebrospinal fluid cell count and an elevated inorganic phosphorus or total protein, or a normal inorganic phosphorus or total protein and an elevated cell count.

In most instances of poliomyelitis the inorganic phosphorus or total protein values have more of a corroborative value than a diagnostic value; however, there are some cases in which the elevated inorganic phosphorus level, together with the clinical findings, have diagnostic significance, i. e., in which the increase in inorganic phosphorus is the only abnormal finding in the cerebrospinal fluid. The following cases are examples of such findings.

Case 20.—The patient was admitted to the hospital when nasal regurgitation developed after a two-day history of sore throat. The other salient findings were a slight nasal discharge and injected throat. Two spinal punctures were done: one on admission and the other 13 days later. Both revealed normal cell counts, 6 and 2 leucocytes per cubic millimeter, respectively; normal total protein values, 21 and 20 mg. per 100 ml., and negative reactions for globulin. The inorganic phosphorus was elevated in both specimens: 1.9 and 2.0 mg. per 100 ml. The patient was maintained on gavage feedings (including, among other foods, those rich in phosphorus) for four days; the tube was removed when the patient became able to swallow. She made an uneventful recovery.

Case 18.—A 5-year-old boy was admitted to the hospital with a two-day history of fever, restlessness, and headache. On admission his temperature was 103.8 F; his pulse was 140 per minute, and his respirations were 24 per minute. His pharynx was slightly injected. There was moderate nuchal and spinal rigidity and hyperactive reflexes in the lower extremities. On the following day he had marked weakness of the abdominal muscles and spasm of the back. On admission the cerebrospinal fluid revealed 1.5 mg. of inorganic phosphorus per 100 ml., 30 leucocytes per cubic millimeter, 30 mg. of total protein per 100 ml., a negative reaction for globulin, and 77 mg. of sugar per 100 ml. This patient evidenced marked involvement of the hypothalamus, dramatically illustrated by the degree of hyperpyrexia, with temperatures ranging from 108 to 104 F for nine weeks, a temperature of 99 F being attained only on the application of cooling enemas, alcohol sponges and ice sponges, etc. The cerebrospinal fluid pleocytosis subsided during this time, cell counts 11 days and 3 weeks after admission giving values of 0. The values for total protein were also normal, 24 and 22 mg. per 100 ml.; the sugar level continued normal, 91 and 81 mg. per 100 ml., and the reaction for globulin remained negative. Only the inorganic phosphorus levels revealed evidence of central nervous system involvement, being 2.1 and 2.0 mg. per 100 ml. During this period the patient evinced extensive involvement of the brain; he was comatose and exhibited frequent convulsive seizures and tremors in all extremities and spastic flexion in all joints. He was treated with gamma globulin and adjunctive therapy and was maintained on gavage feedings, which included, among other foods, those rich in phosphorus.[34] He went on to eventual recovery.

There were eight cases (Cases 19, 31, 52, 59, 63, 72, 73, and 99) of nonparalytic polio-

myelitis in which, on admission, there were clinical symptoms of central nervous system involvement and an elevated cerebrospinal fluid inorganic phosphorus level but a normal cell count. In addition, it is interesting to note that the sister (Case 69) of Case 72 was admitted to the hospital at the same time but with a cerebrospinal fluid cell count of 44 per cubic millimeter (Table 1).

Why is the inorganic phosphorus content of the cerebrospinal fluid increased during acute poliomyelitis?

Perhaps one of the most likely sources of this increase in inorganic phosphorus in poliomyelitis, as deduced from observations of human autopsy material, is the breakdown of central nervous system tissue, as evidenced by destructive changes in the spinal cord, the changes being manifested by chromatolysis of the ganglion cells, particularly in the anterior horns (Rissler[35]; Savini-Castano and Savini[36]; Bodian[37]), degeneration of the axis cylinders (Hassin[38]; Bodian[37]), demyelination (Blanton[39]; Luhan[40]; Neubuerger[41]), the presence of fat-laden gitter cells (Baker[42]; Neubuerger[41]), and necrosis due to inflammation (Baker[42]; Wickman[43]; Craw[44]; Barnhart, Rhines, McCarter, and Magoun[45]). These lesions are not always confined to the spinal cord but may be widely distributed in the brain (Bodian[46]; Baker[42]; Hassin[38]; Peers and Lillie[47]), the parts mostly affected being the motor areas of the cerebral cortex, the vermis of the cerebellum, the midbrain, the hypothalamus, the thalamus, the substantia nigra, the globus pallidus, and the reticular formation of the pons and medulla, the brain stem as far rostral as the thalamus bearing the brunt of the pathologic changes in the cerebrum. There occurs, therefore, during the acute stage of the disease extensive nerve tissue destruction. Central nervous system tissue, both gray and white matter, is particularly rich in phosphorus-containing compounds, the mineral constituents of the brain, in order of decreasing concentration, being carbon, hydrogen, oxygen, nitrogen, phosphorus, chlorine, magnesium, sodium, potassium, iron, calcium, copper, and manganese (Alexander and Myerson[48]). Phosphorus, in the form of phosphate, is an integral part of the molecule in lecithins, cephalins, sphingomyelin, nucleoproteins, ATP, ADP, phosphocreatine, phosphoglucomutase, etc. It is, therefore, entirely conceivable that the increased inorganic phosphorus in the cerebrospinal fluid has its origin in the destructive processes caused by the poliomyelitis virus, or during the propagation of poliomyelitis virus on phosphorus-containing central nervous system tissue.

One might consider the possibility that the inorganic phosphorus diffuses from the blood serum to the cerebrospinal fluid because of pathological alteration of the hematoencephalic interchange caused by invasion of the central nervous system by poliomyelitis virus. (The term "interchange" in the phrase "hematoencephalic interchange" is used rather than "barrier" because the latter is archaic in the modern-day concept of selective absorption by tissue; the use of "barrier" in cerebrospinal fluid dynamics has evoked the hypothesis of one-way passage of substances—from blood to cerebrospinal fluid—the passage of central nervous system debris from cerebrospinal fluid to serum in acute diseases, such as poliomyelitis, and in degenerative diseases having received but scant attention. Others, e. g., Broman,[49] have preferred the use of the term "selective permeability of the cerebral vessels" rather than "blood-brain barrier.") Or, the increase in cerebrospinal fluid inorganic phosphorus might be due to the adjustment of the Donnan equilibrium between the cerebrospinal fluid and the serum during poliomyelitis.

Then, again, the function of the increased inorganic phosphorus ions might be to maintain a normal cerebrospinal fluid pH during the siege of poliomyelitis in the central nervous system.

What is the fate of the increased cerebrospinal fluid inorganic phosphorus? Bakay and Lindberg,[50] in 1948, injecting sodium phosphate containing radioactive phosphorus (P^{32}) into the cisterna magna of rabbits, determined that the highest concentration of radioactive phosphorus appears within the

first 10 minutes after injection, falling rapidly thereafter. Employing the same technique on cats, Sacks and Culbreth [51] found that three-fifths of the tracer appears to be absorbed into the general circulation four hours after injection. Adams [52] and Maass and Adams [53] found that when inorganic phosphate with radioactive phosphorus (P^{32}) was injected into the cerebrospinal fluid of normal dogs, the serum uptake was surprisingly rapid—initially high during the first five minutes and then declining rapidly. In patients undergoing prefrontal lobotomy, whose absorptive processes were presumably normal, Adams [52] found that the maximum level of radioactive phosphorus in the blood occurred 20 to 30 minutes after injections into a lateral ventricle, indicating rapid serum uptake of phosphate ion from the cerebrospinal fluid. Although the exact site at which the cerebrospinal fluid phosphate ion enters the vascular system remains debatable, the best available evidence indicates that the cerebrospinal fluid is probably ultimately absorbed into the major venous sinuses. Whether the absorption takes place by the perineural lymphatics, arachnoid villi, perivascular spaces, choroid plexus, ependymal lining in the ventricles, or capillaries, and possibly the small veins of the pia-arachnoid distal to the Pacchionian bodies, as suggested by Adams [52] and Maass and Adams,[53] the inference is that phosphate ion is transferred from the cerebrospinal fluid to the serum with relative rapidity. It might then follow, in acute poliomyelitis, that the elevated cerebrospinal fluid inorganic phosphorus would diffuse fairly quickly through the hematoencephalic interchange to the serum, and that evidence of such interchange of the phosphate ion would be found in the serum. Our findings show that the values for inorganic phosphorus in acute poliomyelitis in blood, obtained on the day of admission to the hospital, were seemingly within normal limits (Table 2). In contrast with these results were the findings of studies in measles encephalitis and encephalomyelitis (Odessky and associates [54]), in which we found hypophosphatemia concomitant with elevated cerebrospinal fluid inorganic phosphorus. In acute poliomyelitis, usually a period of lowered food intake (consequently lowered phosphorus intake) and increased metabolism, the multiplicity of variables—elevated level of cerebrospinal fluid inorganic phosphorus, which may be produced by one or several factors, as previously hypothesized; the difficulty in diagnosing poliomyelitis early (as compared with, for instance, measles encephalitis and encephalomyelitis); the mo-

TABLE 2.—*Comparison of Inorganic Phosphorus in the Cerebrospinal Fluid and in the Serum*

Case No.	Age, Yr.	CSF Inorganic Phosphorus, Mg. per 100 Ml.	Serum Inorganic Phosphorus, Mg. per 100 Ml.	CSF/Serum, Ratio*	Condition at Time of Discharge†
		Under 14 Years of Age			
1	1	1.9	4.8	0.40	++
6	3	1.9	5.2	0.37	++
13	4	1.9	5.3	0.36	+
17	4	1.9	4.8	0.40	+
18	4	1.5	4.6	0.33	++
		2.1	5.2	0.40	11 days later
20	5	1.9	5.4	0.35	0
28	5	2.0	3.9	0.51	0
29	5	2.0	4.5	0.44	++
32	5	1.7	4.5	0.38	++
35	6	2.7	5.4	0.50	0
38	7	1.7	4.2	0.40	0
40	7	2.0	3.5	0.57	0
42	7	1.9	3.8	0.50	++
49	8	2.2	5.1	0.43	0
52	8	2.1	4.8	0.44	0
53	9	3.1	4.3	0.72	+
54	9	1.8	4.8	0.38	0
58	9	1.9	3.5	0.54	Died 4 days later
59	9	2.0	4.8	0.42	0
61	11	2.4	4.1	0.59	++
64	11	2.3	4.5	0.51	Died 6 days later
68	12	2.1	4.3	0.49	0
		Adults			
84	20	2.0	4.0	0.50	Died 10 hr. later
87	21	2.2	2.8	0.79	++
91	22	1.5	2.1	0.71	+++
93	23	2.0	3.4	0.59	Died 2 days later
96	24	1.8	2.4	0.75	0
97	24	2.1	4.8	0.44	+++
100	29	2.0	4.1	0.49	Died 18 hr. later

* Ratio: Range for normal children

$$\frac{\text{CSF inorganic phosphorus}^{\,2}}{\text{Serum inorganic phosphorus}^{\,54}} \quad 1.2 \text{ to } \frac{2.0}{4.0}, \text{ or } 0.18\text{-}0.50.$$

Ratio: Range for normal adults

$$\frac{\text{CSF inorganic phosphorus}^{\,2}}{\text{Serum inorganic phosphorus}^{\,55}} \quad \frac{0.8}{4.4} \text{ to } \frac{2.0}{2.5}, \text{ or } 0.18\text{-}0.80.$$

† Symbols indicate the patient categories as in Table 1.

bilization of phosphorus from bone, etc.—leaves the problem of serum inorganic phosphorus open for future investigation. Nevertheless, because the cerebrospinal fluid inorganic phosphorus was definitely elevated in 44% of our patients, the ratios of cerebrospinal fluid to serum inorganic phosphorus (Table 2) for 9 of 22 patients (41%) under 14 years of age were definitely increased, and for 3 of 7 cases (43%) in the 20- to 29-year age group, on the upper limit of normal. The extremes of the ratio for patients under 14 years of age are 0.18 to 0.50, and for adults, 0.18 to 0.80 (Table 2). The normal values for the average ratio for adults in nonsuppurative diseases is stated to be about 0.38 by Merritt and Bauer.[56] We found a similar elevation in the ratio for measles encephalitis and encephalomyelitis in children, seven out of eight of whom had ratios above the limit of normal (Odessky and associates[54]).

Experimental work with poliomyelitic brain and spinal cord tissue has disclosed that metabolism of phosphorus compounds in the central nervous system is significantly altered from that of normal tissue.

It was shown by Anderson, Gemzell, Gemzell, Bolin, and Samuels[57] that infection with the Lansing strain of poliomyelitis virus produces significant changes in the rate of turnover of phosphorus in the inorganic phosphate and total acid-soluble organic phosphate fraction, as against that for control animals. Anderson and colleagues found, as a result of intracerebral inoculation of healthy rhesus monkeys, that inorganic phosphate fractions in the spinal cord, medulla, pons, and cerebellum were significantly altered from those of control animals: The spinal cord and cerebellum showed initial decreases in inorganic phosphate, but after clinical manifestations of poliomyelitis, such as weakness, tremors, or paralysis, the tissue specimens revealed marked increases in inorganic phosphate.

Kabat[58] found that brains from mice paralyzed with the Lansing strain of poliomyelitis virus showed an increase in the acid-soluble phosphorus fractions, while phosphocreatine and residual organic phosphate fractions decreased. Kabat concluded that marked changes in acid-soluble phosphorus compounds suggest the possibility of considerable interference with energy mechanisms and carbohydrate metabolism of neurons by poliomyelitis infection.

During the regeneration of sectioned axons of the anterior horns, a process similar to that of central chromatolysis of the recovery phase in nerve cells in poliomyelitis (Bodian[37]), Bodian and Mellors[59] found that the value for phosphocreatine phosphorus was significantly and appreciably less than that of normal gray matter. The sum of acid-hydrolyzable and inorganic phosphate was unchanged in regenerating, as compared with normal, anterior horns.

Abnormal phosphorus metabolism is not, however, limited exclusively to acute poliomyelitis but probably occurs in many acute, chronic, and degenerative diseases of the central nervous system. For instance, we have found elevated cerebrospinal fluid inorganic phosphorus values in measles encephalitis and encephalomyelitis,[54] mumps meningoencephalitis,[60] varicella encephalitis, and influenza meningitis.[61] Markedly increased values of cerebrospinal fluid inorganic phosphorus are well known in tuberculous meningitis and, to a less extent, in other meningitides.‡

In conclusion, since there is clinical and experimental evidence of pathologic phosphorus metabolism, the treatment of acute poliomyelitis should include, among other substances, a source of readily available phosphorus in order that the central nervous system might be provided with the necessary constituents for its maintenance and recovery from the disease.

SUMMARY AND CONCLUSIONS

Cerebrospinal fluid inorganic phosphorus was determined in 110 fluids from 104 randomly selected patients in the acute stage of typical poliomyelitis and was found to be

‡ References 4 and 62 through 64.

statistically elevated, as compared with values for control patients. The mean value for inorganic phosphorus was 1.9 mg. per 100 ml. of cerebrospinal fluid (standard deviation ± 0.36; standard error of the mean ± 0.03). The values ranged from 1.1 to 3.1 mg. per 100 ml. Forty-eight values (44%) were definitely elevated, 2.0 mg. per 100 ml., or more, while 62 values (56%) were 1.9 mg. per 100 ml., or less. The relative number of elevated cerebrospinal fluid inorganic phosphorus levels increased as the cytology shifted from polymorphonuclear leucocytes to lymphocytes. There was no correlation between the inorganic phosphorus levels and the ages of the patients, which ranged from 1 to 47 years.

The increased levels of inorganic phosphorus in the cerebrospinal fluid in acute poliomyelitis may be attributed to (*a*) destruction of phosphorus-containing central nervous system tissue; (*b*) diffusion of inorganic phosphorus from the serum to the cerebrospinal fluid by way of the pathologically altered hematoencephalic interchange (the term hematoencephalic "barrier" being considered obsolete, according to the concept of selective absorption in cerebrospinal fluid physiology); (*c*) alteration of the Donnan equilibrium between cerebrospinal fluid and serum; (*d*) necessity for maintaining, as normal as possible, the pH of the cerebrospinal fluid during the acute stage of the disease, and (*e*) direct action of the poliomyelitis virus on specific phosphorus-containing components of the central nervous system.

Cell counts, total protein, globulin, and sugar were determined on all fluids, and the results were compared with the levels of inorganic phosphorus. Direct smears and cultures were also made on every fluid.

We conclude that, although cerebrospinal fluid pleocytosis (a determination no more specific than the inorganic phosphorus level) still remains the best indication of central nervous system invasion of poliomyelitis, the inorganic phosphorus value is of corroborative value, and in some instances has diagnostic value: in one case of bulbar poliomyelitis and in eight cases of nonparalytic poliomyelitis the only abnormal finding in the cerebrospinal fluid indicative of central nervous system involvement was an increased inorganic phosphorus level.

The serum inorganic phosphorus of 29 patients was seemingly within normal limits, the blood and cerebrospinal fluid specimens having been obtained at the same time. For 12 of these patients (41%) the ratio of cerebrospinal fluid inorganic phosphorus to serum inorganic phosphorus was definitely increased or at the upper limit of normal.

In view of the clinical and experimental evidence of pathologic metabolism of phosphorus, one of the most important and one of the largest constituents of the central nervous system, the treatment of patients with poliomyelitis in the acute phase should include a readily available source of phosphorus, among other substances, to provide (*a*) for the normal basal metabolic requirements of the nerve tissue, (*b*) for the increased metabolic rate during poliomyelitis and, in addition, (*c*) for repair of the nerve tissue damaged by the poliomyelitis virus.

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Blood Platelets in Disseminated Sclerosis

Quantitative Variations in Peripheral Blood

TORBEN FOG, M.D.
INGRID KRISTENSEN
and
HANS FR. HELWEG-LARSEN, M.D., M.P.H.,
Copenhagen

The peripheral blood of patients with disseminated sclerosis has been examined with a view of studying blood platelet variations. We have concentrated particularly on blood platelet counts for the reason that blood platelet agglutinations have been noted in the blood vessels in encephalomyelitic foci. These agglutinations may, of course, be regarded as agonal, but the possibility of intravital agglutinations exists, and the probability of such a phenomenon would become greater if variations in the total blood platelet system of the organism, with a tendency to increased agglutination, could be demonstrated in patients with the disease. Recognition of the stated agglutinations is a result of the great interest taken in the vascular condition in disseminated sclerosis, in which the degenerative and reactive tissue changes have been found to bear a pronounced relation to the venous system (Putnam,* Broman,[4] Fog,† Haarr [8]).

MATERIAL AND METHODS

The material comprises 103 cases of inactive and 11 cases of active disseminated sclerosis, among which latter were 2 with neuromyelitis optica and 1 with bilateral retrobulbar neuritis. The justification for including these three cases will not be discussed in this place, but reference may be made to Fog.[5] Blood platelet counts have been made on blood from a greater number of patients with disseminated sclerosis, but only 103 inactive cases have been included in our statistical calculations, because we have aimed at as "pure" a series as possible; i. e., we have excluded the cases with complications, in the form of infections, and the like. Some of the cases omitted are described further in connection with the demonstration of the curves.

As controls, we used 30 patients with other neurological disorders, as well as 10 normal subjects "in activity," i. e., nurses and physicians, from whom blood samples were withdrawn while the subjects were at work. In the case of the patients, we aimed at basic conditions of blood sampling. Blood was withdrawn a few hours after the patient had eaten a light breakfast, and, as far as possible, always with the patient in bed. Eating and moving seem, however, to have no influence on the number of blood platelets.

The technique employed was that suggested by Heinild.[9]

Practically all the counts were made by one of us (I. K.).

It is absolutely necessary that the counting chambers be in order; i. e., among other things, the volume must actually correspond to that indicated on the chamber. Chart 1 illustrates the necessity of this. This graph represents counts in 10 chambers (5 tubes with 2 chambers each) on four different days. For comparison, we used the two counting chambers in which the series under review was counted. In no less than six counting chambers the number of blood platelets was twice as high as that in the four others plus the two control chambers. In other words, the volume was much greater in the majority of the chambers than in the two "old" and tested counting chambers. The counting chambers, therefore, ought first to be tested on one or more normal subjects by serial counts.

The Charts show the numbers of blood platelets per cubic millimeter of citrated venous plasma from day to day. We did not correct for hemoglobin per cent, as this was normal throughout, and as it was not the absolute blood platelet number that interested us. We counted blood from patients and

From the Neuromedical Department, Rigshospitalet (Prof. Mogens Fog) and from the University Institute for Human Genetics (Prof. Tage Kemp).

* References 1 through 3.

† References 5 through 7.

normal subjects every day except Sundays and holidays, through periods ranging from a few days up to nine months, in most cases for about one month. No consideration was taken of menstruation. The variations during menses were generally so small that they played no part in the present series. We found as many normal curves as fluctuating curves during the menses. Wright,[10] who made a series of blood platelet counts on subjects during menstruation, found no variation whatever in number or agglutinability.

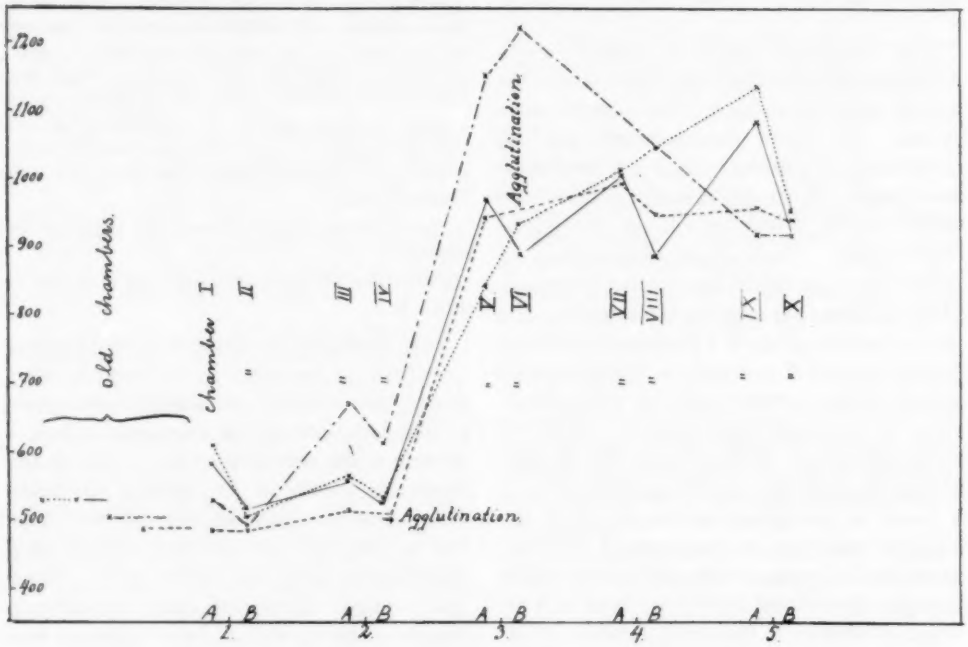

Chart 1

Our patients likewise presented only small variations during menses (not over 200,000 platelets from the mean). One patient constituted an exception and has therefore been excluded. The 103 patients with disseminated sclerosis represent 3153 counts, and the control and normal series, 791 counts.

The variation of the thrombocyte counts is expressed by their standard deviation, or by mean square, the counts for each experimental subject or patient being grouped in intervals of 50,000 thrombocytes per cubic millimeter. There are here different kinds of variation. The variation determined by experimental condition may, according to Heinild, be expressed by the standard deviation $1.2\times\sqrt{M}$, where M is the result of a single count measured in 1000's. In the present investigation it often seemed lower. A 24-hour variation for single subjects can, according to Heinild, be left out of account. To this variation may be added a day-to-day variation in the same subject, which could be determined in the present investigation. In the case of normal subjects and patients with "inactive" disseminated sclerosis we do not hesitate to express this variation by the standard deviation of the counts, as a count seems independent of the preceding one and as the variations are rather symmetrically distributed around a mean. "Active" disseminated sclerosis, on the other hand, shows, as described below, wave-like fluctuations, within which one count does not seem independent of the preceding one. As we did not preferably choose peaks or bottoms for the counts, we felt justified in using the standard deviation as a measure of this variation, realizing

TABLE 1.—*Pooled Mean Squares and Standard Deviations* for Single Subject of the Four Experimental Groups*

Experimental Group	Mean Square	Standard Deviation	Degrees of Freedom
Normals	32.88	5.73	151
Other neurologic disorders	47.13	6.87	407
Active disseminated sclerosis	124.06	11.14	770
Inactive disseminated sclerosis	61.10	7.82	2,815

* Standard deviation to be multiplied by 10,000, being thus 57,300 for normals.

that the expression obtained served mainly to illustrate the variation numerically, not being very suitable as a basis for continued statistical comparisons.

The results of these determinations appear in Table 1.

It seems a natural procedure, now, to compare, by the F (or v^2) test, the thrombocyte count variations in the individual subjects of the four experimental groups. This has also been done, and the dispersions were all found to differ significantly. The condition for the analysis, namely, that the individual mean squares could be regarded as identical within each experimental group, was not present, however, as demonstrated by the "false χ^2 test." This test showed an accumulation of mean squares around a central value and a greater number of mean squares with very high and very low values than would correspond to a random distribution of the dispersions.

TABLE 2.—*Distribution of Mean Squares of Thrombocyte Counts in the Four Experimental Groups*

Mean Square	Normal	Other Neurologic Disorders	Disseminated Sclerosis	
			Active	Inactive
0- 24	4	9	..	7
25- 49	4	8	1	37
50- 74	2	4	4	33
75- 99	..	1	1	15
100-124	..	1	1	3
125-149	..	1	1	4
150-174	..	..	2	2
175-199	..	..	1	..
.....	..	..	..	..
225-249	..	..	..	1
250-274	..	..	..	1
Total	10	24	11	103

We therefore preferred to present the result of individual dispersions (mean squares) for the different experimental groups in the form of Table 2.

Table 2 illustrates how expressions for individual dispersion are grouped around a somewhat higher value in patients with inactive disseminated sclerosis than in normal subjects and in the group of other neurological disorders. The cases of active multiple sclerosis are distributed around a higher central value than those of inactive sclerosis, as is also suggested by the average individual variation indicated in Table 1.

Although the present series does not allow of a simple comparison between the individual variations of the thrombocyte counts in active disseminated sclerosis patients and in inactive disseminated sclerosis patients, the tendency toward a greater variability of the counts in the active group was so conspicuous that further investigations into this fact must be of value.

TABLE 3.—*Analysis of Variance for the Variation in Thrombocyte Counts for a Normal Subject and the Variation from Subject to Subject*

Source of Variation	Sum of Squares	Mean Square	*d. f.*	Standard Deviation	*f*
Within individual subjects	4,965	32.88	151	5.73	1
From subject to subject	11,010	1,223.33	9	34.97	37.21
Total	15,975		160		

The normal series offered a possibility of comparing the variation within the individual subject with that from subject to subject. The result of this comparison is shown in Table 3.

This analysis showed that among normal subjects the variations in thrombocyte counts is much greater from one subject to the other than in the same subject from day to day.

THROMBOCYTE CURVES

Nonsclerotic Patients.—Chart 2 is a fine "normal thrombocyte curve" for a patient with psychogenic depression.

Chart 3 is a blood platelet curve for a patient with spinal hemorrhage or meningitis following lumbar puncture. A rapid

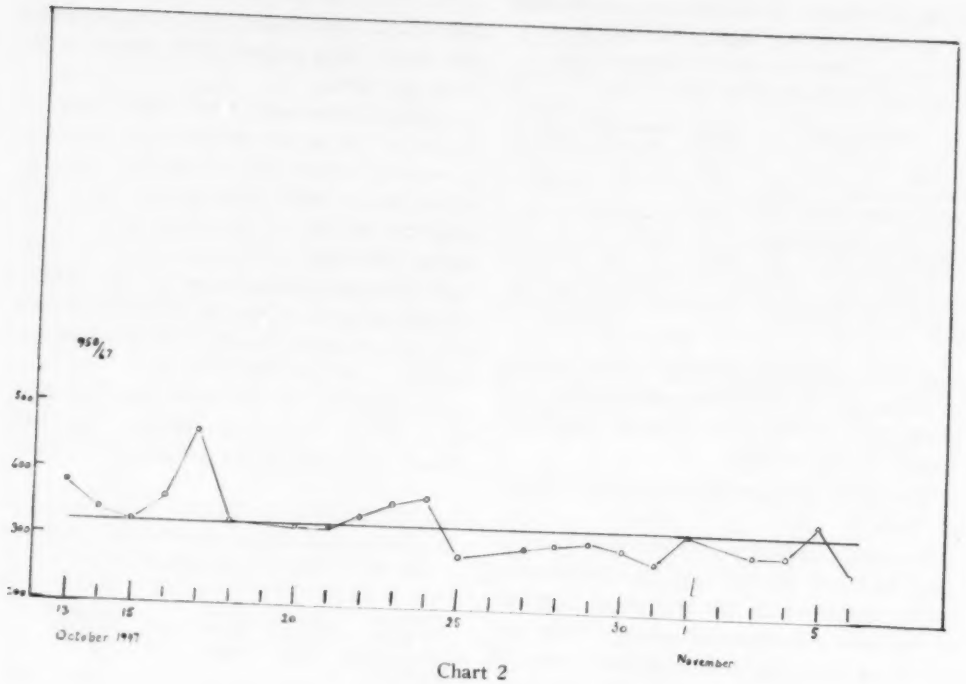

Chart 2

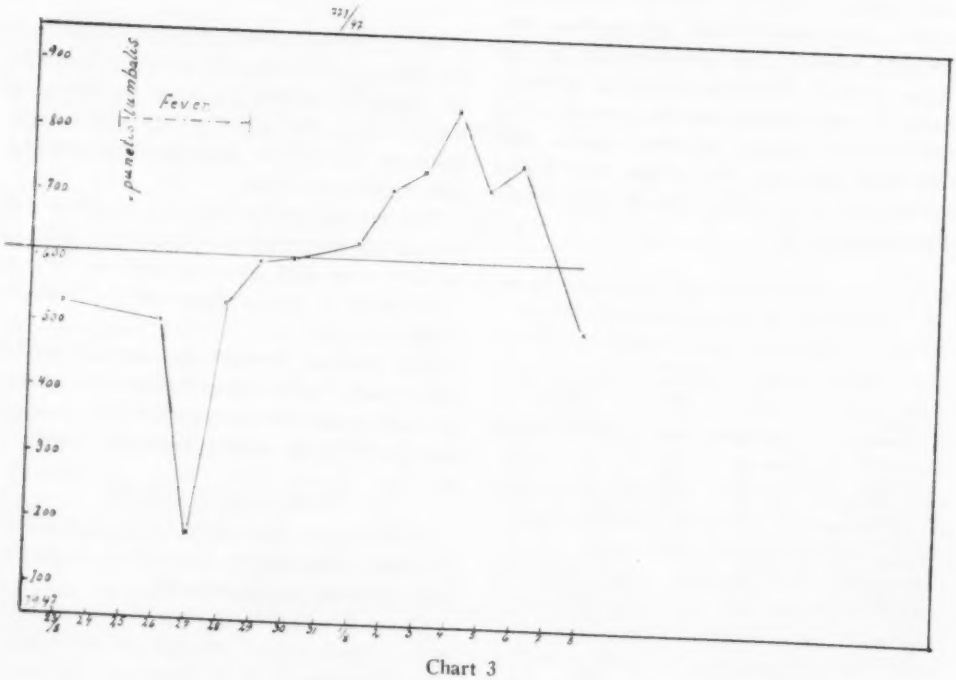

Chart 3

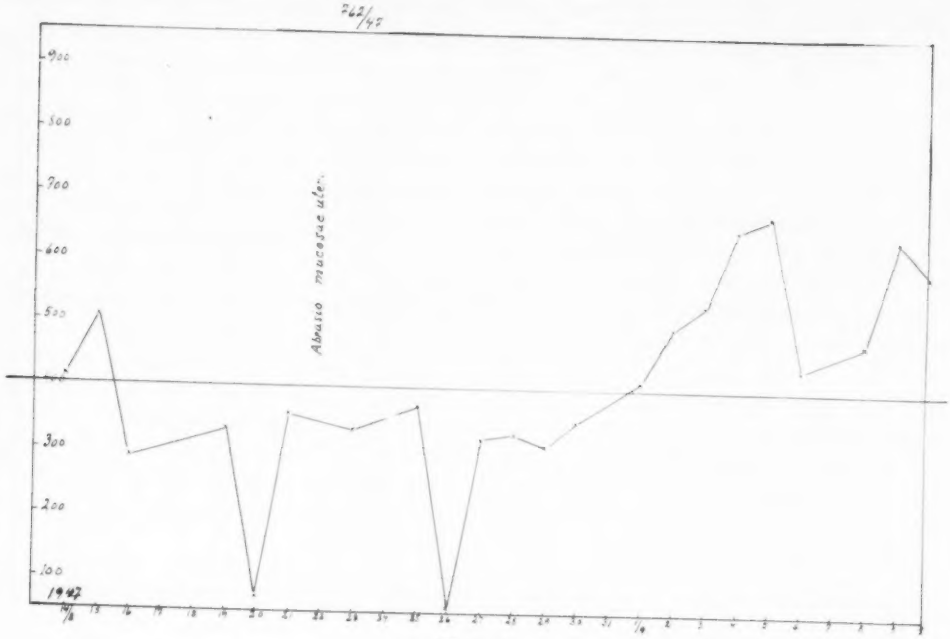

Chart 4

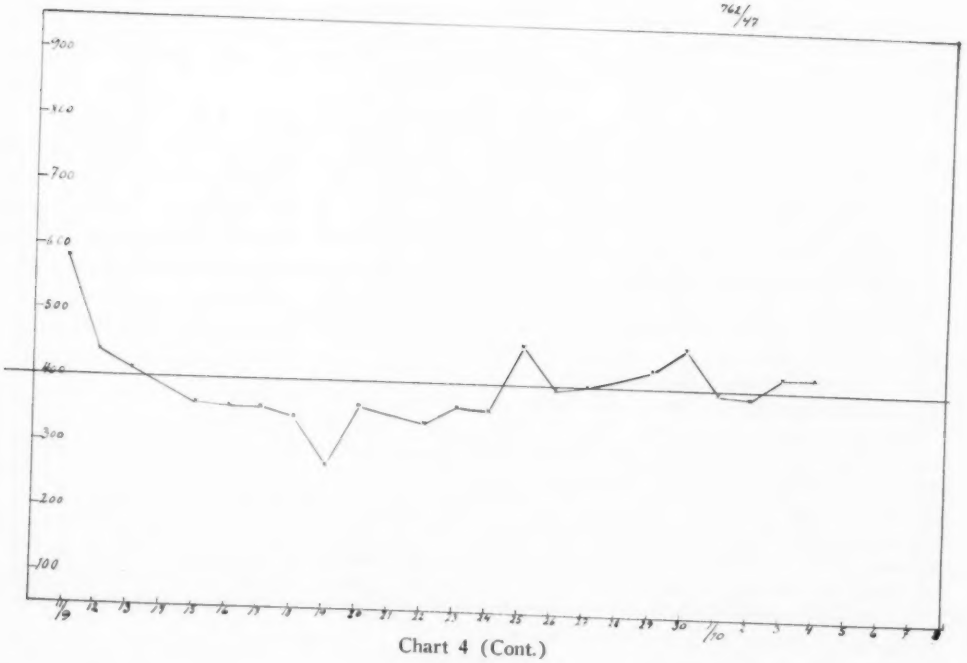

Chart 4 (Cont.)

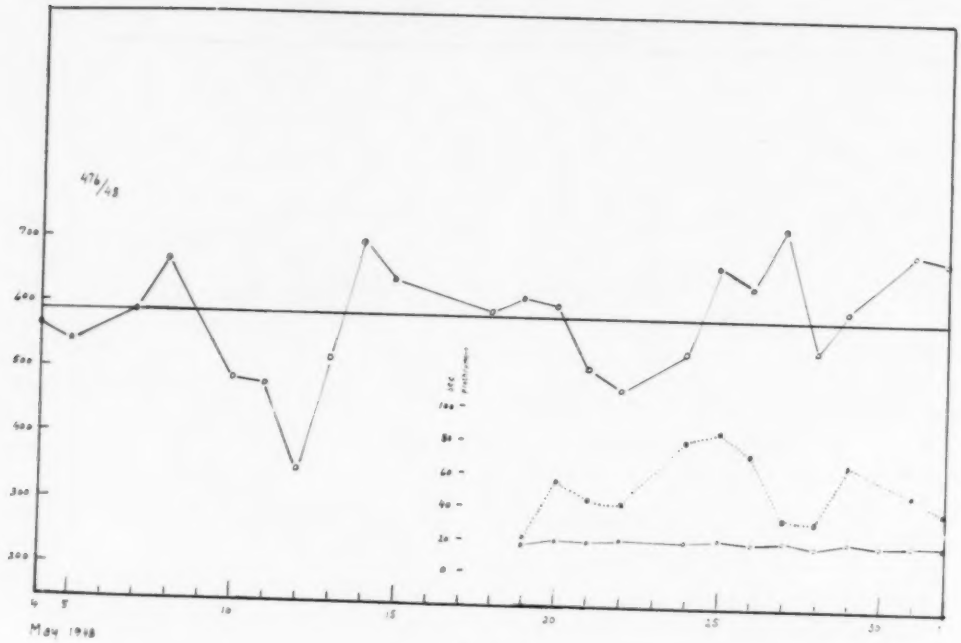

Chart 5

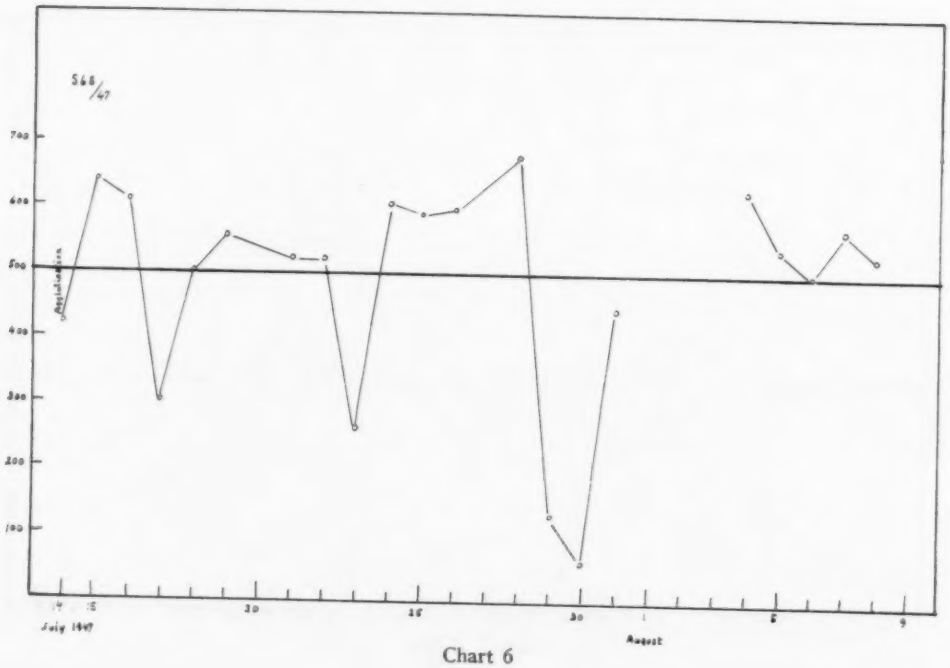

Chart 6

fall during the infection was followed by a prompt rise as soon as the infection had subsided under penicillin treatment. The diagnosis was one of neurastheniform nervosism.

Chart 4 illustrates the postoperative blood platelet rise 10 to 14 days after an operation (uterine excochleation), with a reactive rise of a few weeks' duration, after which the level was fixed again (Wright [10]). The patient had disseminated sclerosis.

Disseminated Sclerosis Patients.—Inactive Disseminated Sclerosis: In the so-called inactive sclerosis cases fluctuations with large waves were usually seen (Chart 5), or a considerable flutter was evident. An interesting observation was that of large negative spikes, occasionally presenting falls toward the bleeding limit. In some of these cases the number of thrombocytes remained low for a few days, but in the majority it rose again the following day (Chart 6). We found no such spikes in the normal or control cases without complications.

Heinild has stated that he has seen similar deep falls of short duration in some of his blood platelet curves plotted during infection and other morbid conditions. The change is therefore hardly "specific." Positive spikes have been seen in both sclerotic and nonsclerotic patients.

The negative spikes seen here, however, are interesting, because definite signs of infection were not demonstrable in the patients. Many of the curves for patients with stationary disseminated sclerosis did not differ from those for normal and control subjects.

Active Disseminated Sclerosis: Nineteen patients have been placed in the active group, which falls in three subgroups:

1. Seven patients in a state of improvement by the time of admission who gave a history of unquestionable activity within a few weeks of admission.

2. Seven patients with the disease in the active phase on admission.

3. Five patients who during a stationary course had a clinical attack, so that the curve could be assessed before, during, and after the attack.

Group 1 (seven patients): In two patients we found fluctuations reminiscent of those in the more stationary cases; in five patients, a chiefly horizontal course, but with deep falls and spontaneous agglutinations in the counting chamber, and in two, changes of level. By change of level we understand a significant difference between the initial and the final level. The two last patients presented a high initial level and a low final level. They may, therefore, have been at the end of the reactive phase by the time the curve was started. One of them (Case 60) was in a state of definite clinical improvement when the plotting of the curve was started.

Group 2 (seven patients): In one case (Case 20) the curve is not worth much, being often broken, with large intervals, during which, unfortunately, no counts were made. In a bad phase there was evident a falling tendency toward an approaching attack, during which the curve was not plotted. On the fifth day after this attack, which clinically had the character of a grave shock, the blood platelet count was very high, and the patient improved rapidly.

CASE 32.—A man, aged 24, who within a few months had two very severe bulbar attacks, of about one or two months' duration, after which he recovered completely and has been well since (with sequelae).

He had had an attack 14 days before his first admission but was rapidly improving on admission. The curve showed a fairly low initial level, as compared with the final level. Six weeks later he experienced another acute attack. He was immediately admitted, and during this stay there was rapidly progressive exacerbation. At a certain point he was almost moribund. His blood platelet curve displayed no abnormality during this attack. It could be characterized as almost a normal curve; but after beginning improvement we saw a marked rise, to twice the initial level. Evidently, the apparently normal curve actually represented a phase of depression. The analogy with Heinild's hepatitis curve is obvious. Heinild notes that in cases of hepatitis he has seen the reactive rise lag far behind the initial extended depression curve. The inconsiderable reactive rise in this case after the first attack may, perhaps, be taken as a sign that the patient was still in the active phase. This view is supported by the recurrence six weeks later. Since the final pronounced reactive rise, the patient has been well for several years. We may not have recorded the first reactive

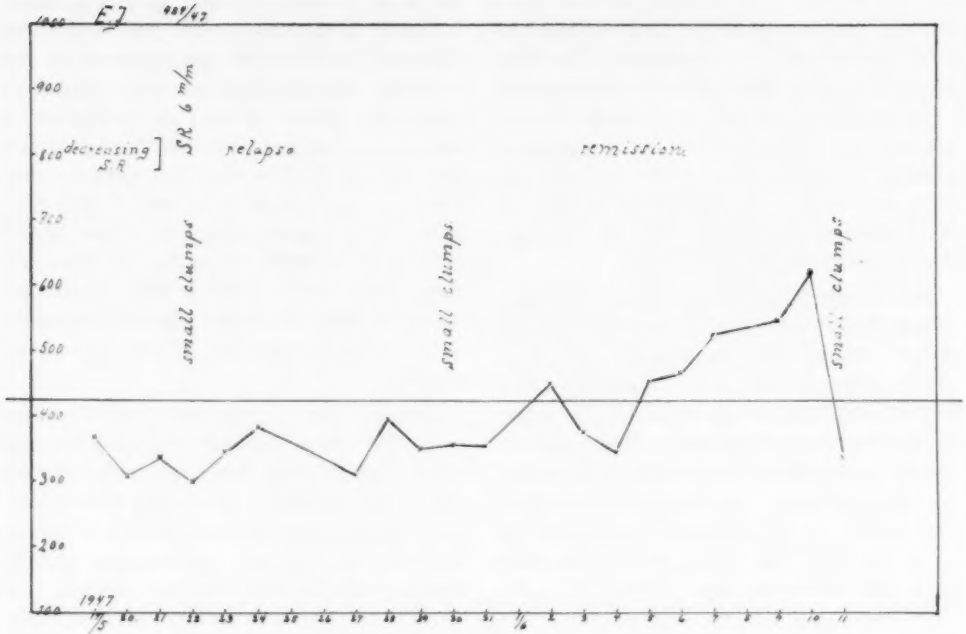

Chart 7

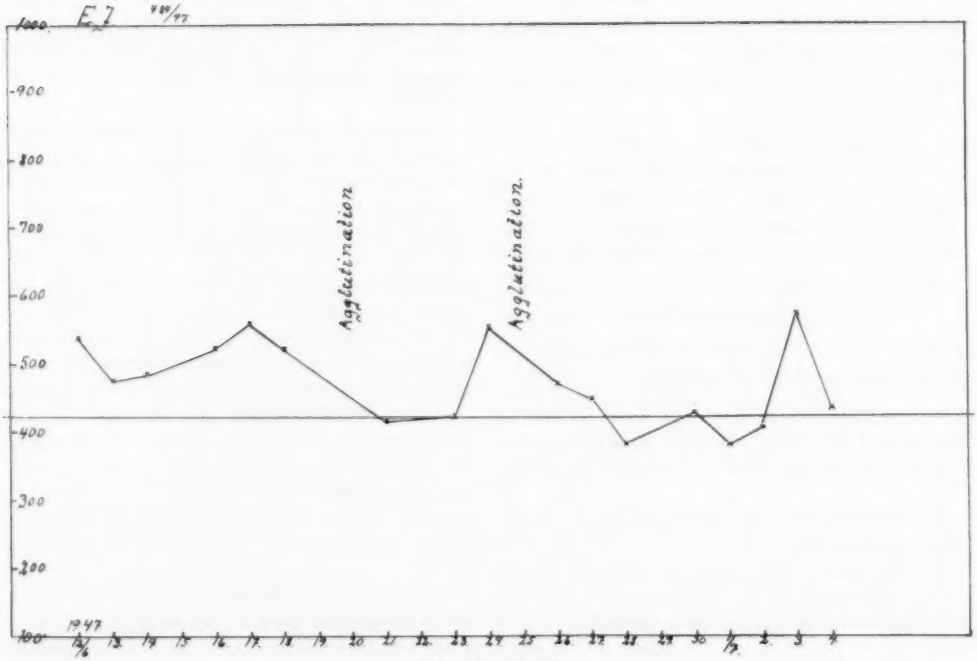

Chart 7 (Cont.)

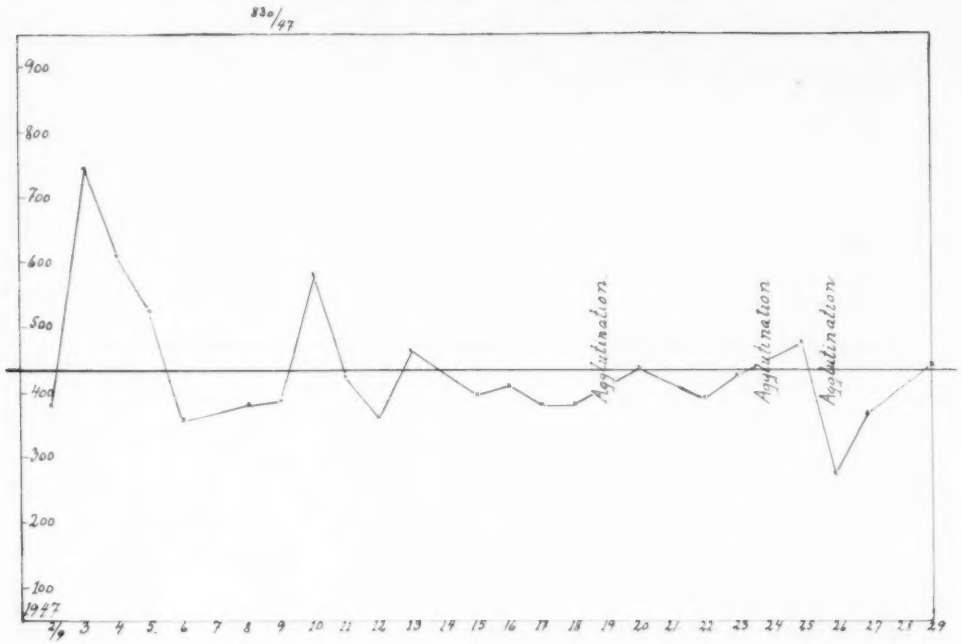

Chart 8

rise, or the last reactive rise may have been high because of the intensity of the attack.

Case 36.—A girl, aged 17, in a protracted bad phase of nearly 12 months' duration. The curve presented great fluctuations. On admission she was in a poor state, but soon improved. The curve showed a low initial level and a high final level, as well as deep falls and spontaneous agglutinations. She has since experienced repeated attacks, but each time with shorter relapses.

Case 52 (Chart 7).—A man with neuromyelitis optica. This patient has been included in Group 2, because he had a minor recurrence of his optic neuritis while in the hospital. His signs and symptoms were typical of neuromyelitis optica. On admission he was improving from the neuromyelitis and the sedimentation rate was falling. The blood platelet level at this time was rather low, with agglutinations and with a very even course of the curve. In this fairly stationary phase a scotoma developed, as a sign of recurrence. With a rise of the blood platelet curve marked improvement followed, during which a reactive rise, back to the normal level, was seen. The curve was thus in principle reminiscent of a blood platelet curve during infection, though the patient displayed no signs of infection. The sedimentation rate had even returned to normal.

Case 64.—Symptoms of activity during the period preceding the patient's admission, and fresh symptoms on the day of admission (Chart 8). On the day of admission the blood platelets showed a low level as compared with the counts on the following three days. The initial high phase the next three days, with a steadily falling tendency, suggested a reactive rise, which was borne out by the fact that she had no fresh signs or symptoms during her stay. The curve now settled to a fine level, as a normal curve, with agglutinations.

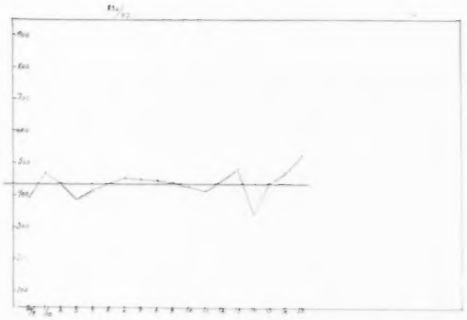

Chart 8 (Cont.)

Case 97.—A man, aged 26, was admitted with very grave symptoms, which had been developing over the course of months. His disease ran a rapidly progressive course in the hospital, with diffuse symptoms over many weeks. The curve plotted for this patient was the longest one of them all, com-

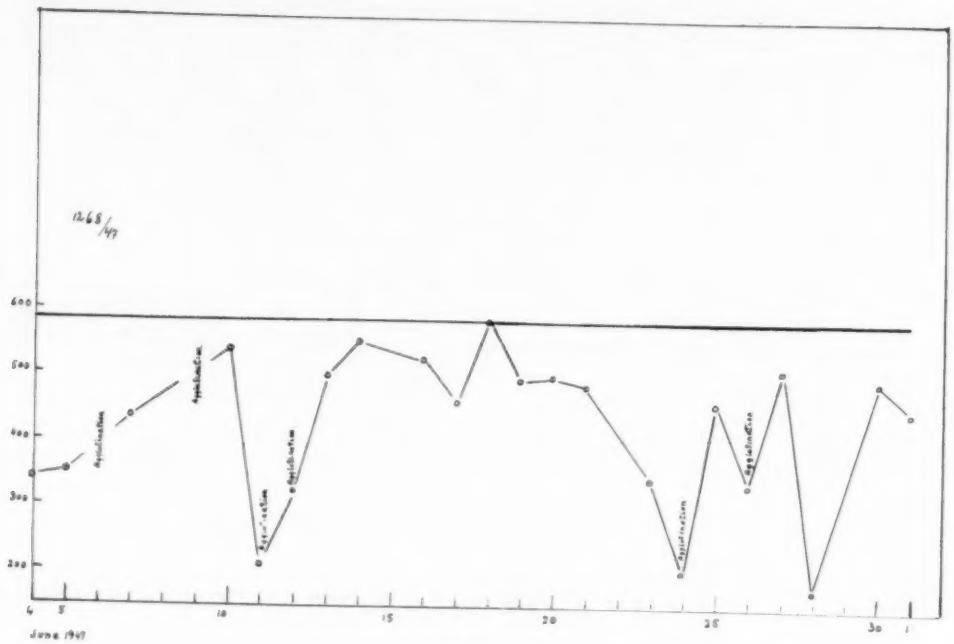

Chart 9

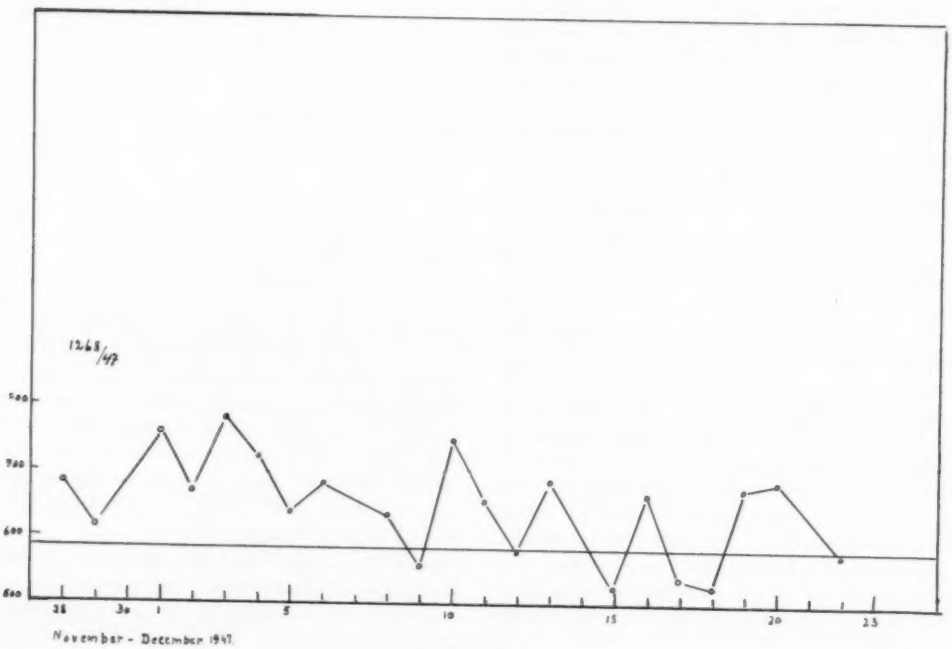

Chart 10

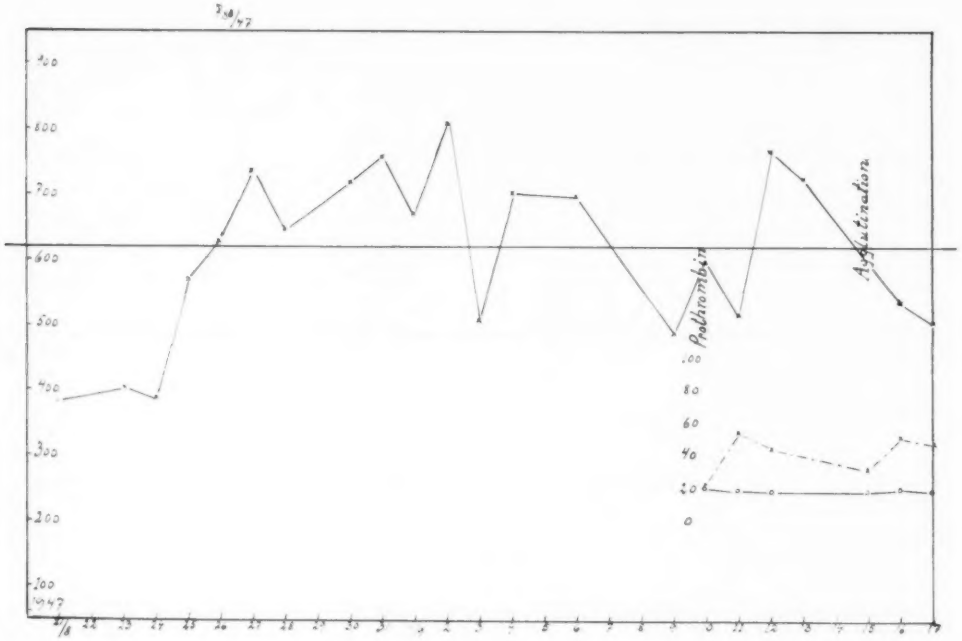

Chart 11

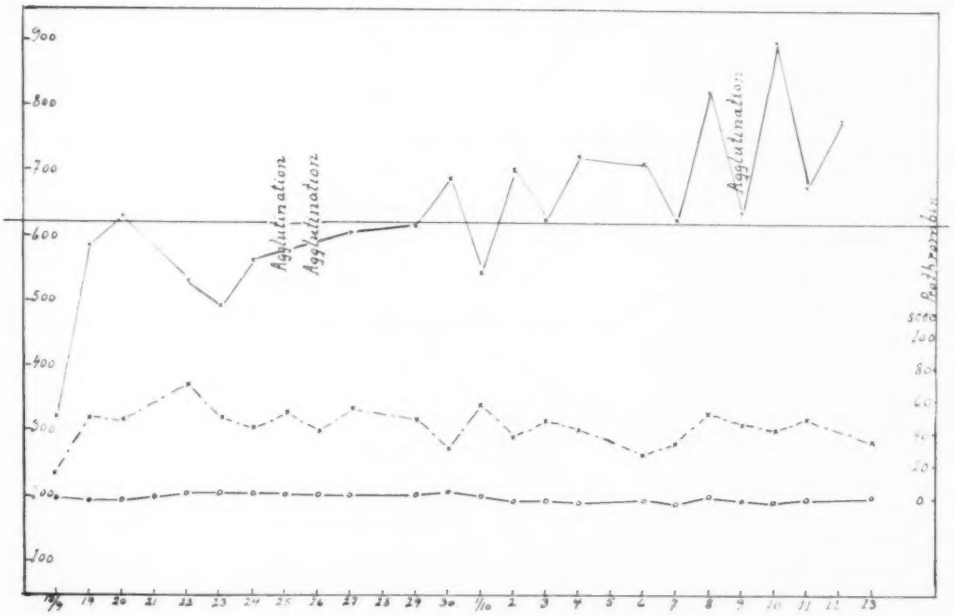

Chart 11 (Cont.)

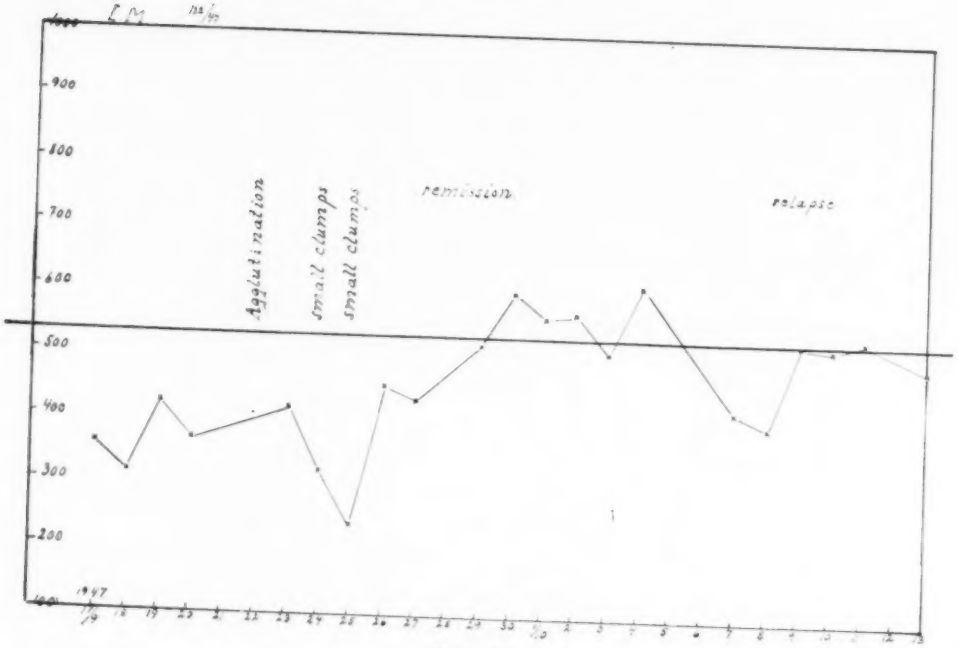

Chart 12

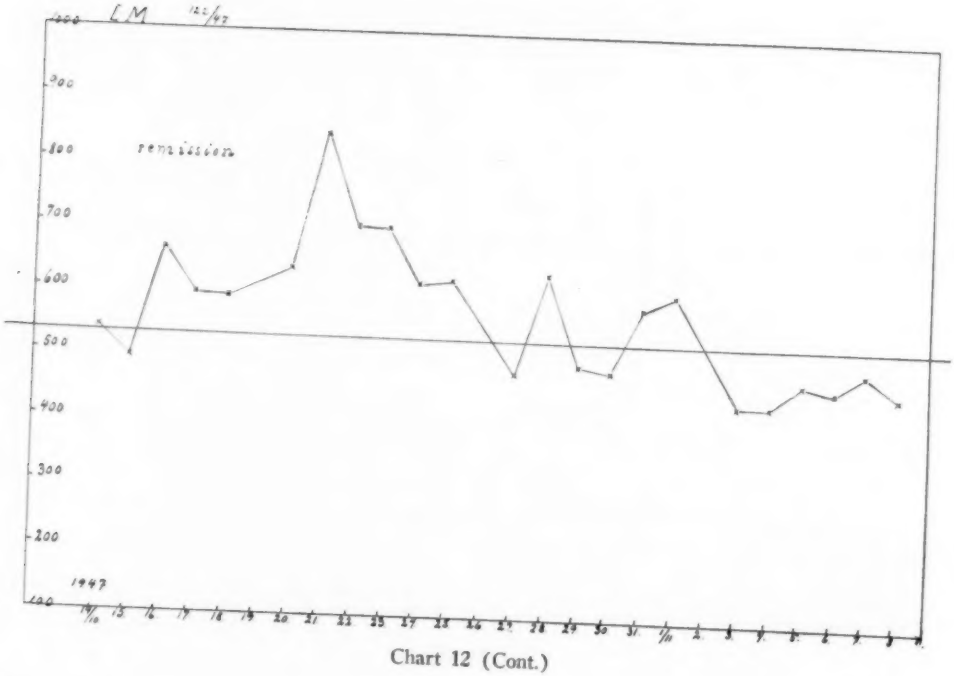

Chart 12 (Cont.)

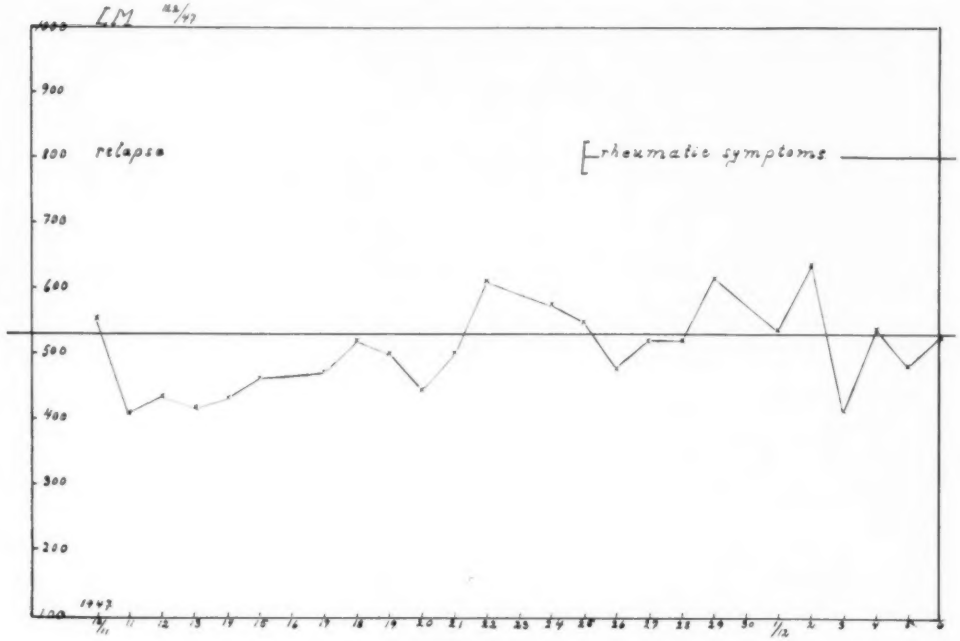

Chart 13

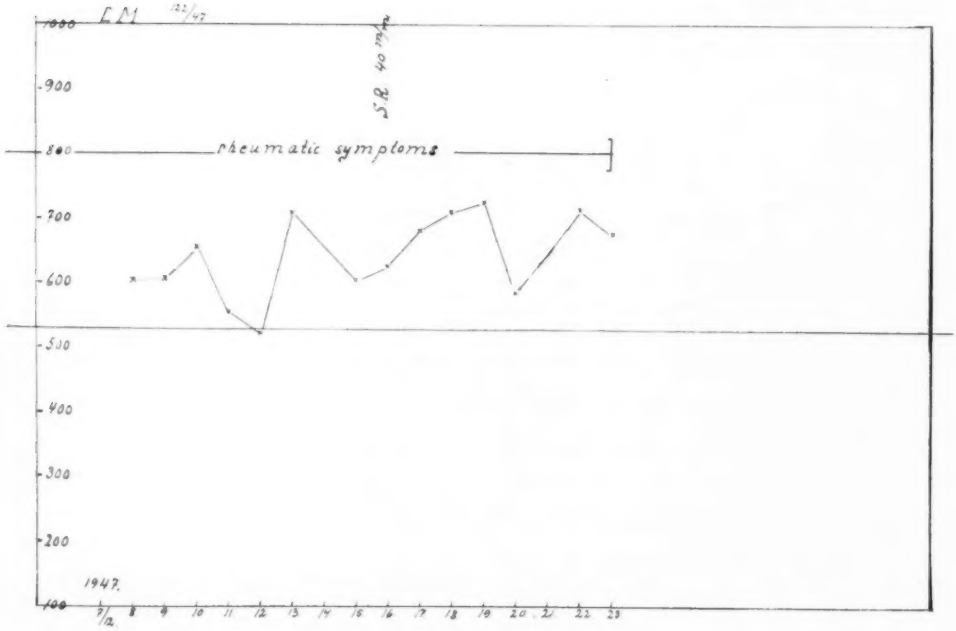

Chart 13 (Cont.)

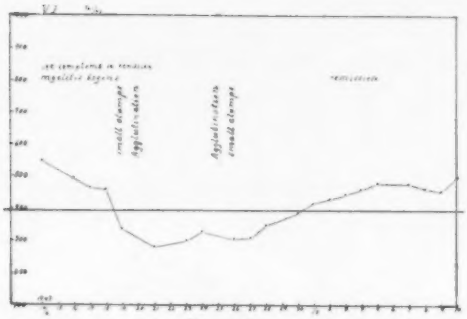

Chart 14

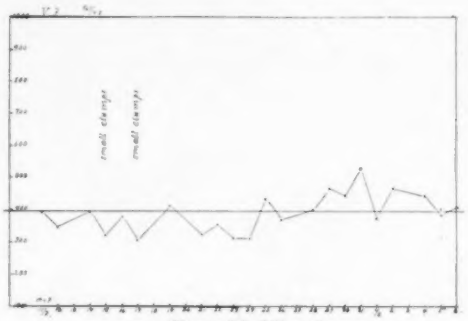

Chart 14 (Cont.)

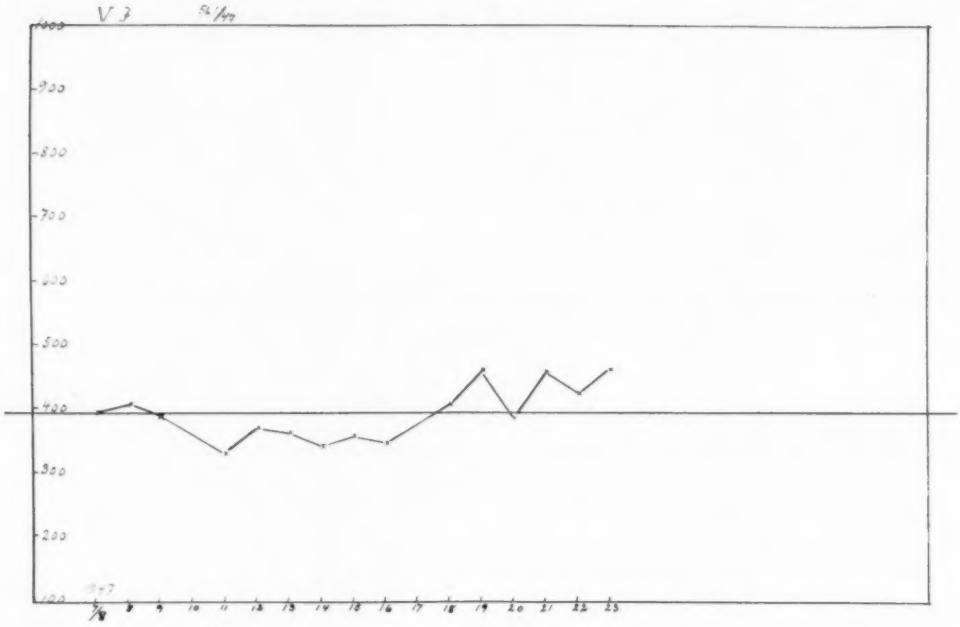

Chart 15

prising 204 counts during the first stay and 37 counts during the second. For lack of space, we present only a single curve from the initial phase (Chart 9). We recorded a low initial level, which soon rose a little, but remained under the mean value for all 204 counts. In this phase there was a considerable number of spontaneous agglutinations. Chart 10 represents the curve five to six months later, when the condition had become fairly stationary. Here values above the mean were recorded; the fluctuations were within the normal range, and the agglutinations had ceased. During the intervening period agglutinations were seen here and there and there were great fluctuations above the norm, while the level showed a slow tendency to rise. The course during all these months was rather stationary with fluctuations, but without definite clinical changes of a more massive nature.

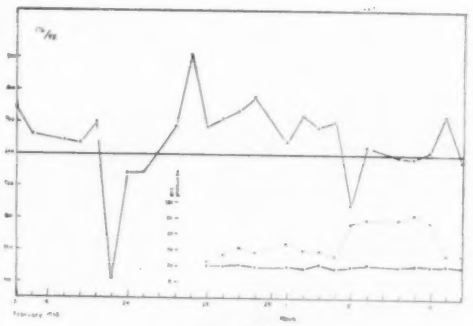

Chart 16

Case 62.—A man, aged 32, who experienced a severe, protracted, progressive attack, which soon after his discharge led to complete disability. The curve showed very great unsystematic changes of level (Chart 11).

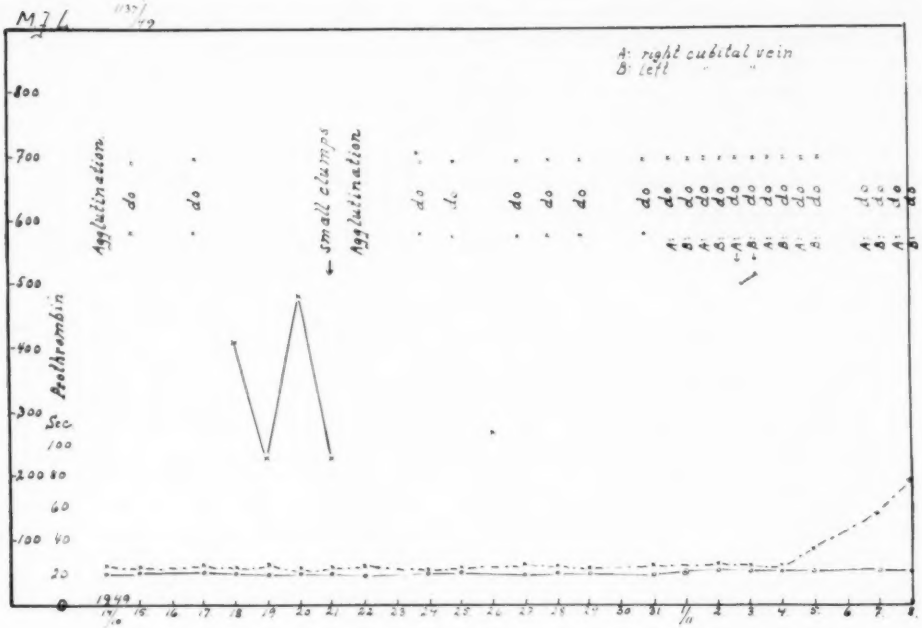

Chart 17

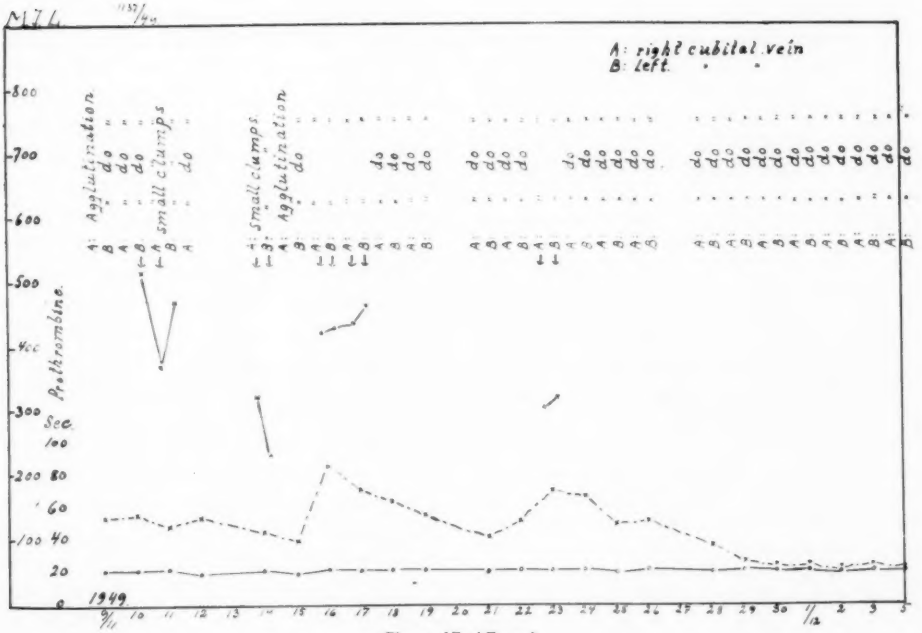

Chart 17 (Cont.)

Five of these seven curves thus all give the same picture. One curve was too broken for assessment. The curves show a tendency to a fairly low level during activity, with or without spontaneous agglutinations, and a reactive rise during definite clinical improvement. The curves differ from ordinary blood platelet curves during infection by being more extended. This applies to the curves for Cases 97, 52, and 32, while those for both Cases 36 and 64 are short, corresponding to clinically short attacks.

Group 3: Case 30.—A young girl suffering from typical and pronounced disseminated sclerosis with polymorphous diffuse symptoms. The curve as a whole showed a fairly low initial level. In this phase, in which the level differed from the final counts by 200,000 to 300,000, and in which the lowest part of the curve occurred, the patient had a definite attack with symptoms from the spinal cord (paralysis of one leg), as well as symptoms of retrobulbar neuritis. During this attack the curve rose, while the retrobulbar neuritis subsided. Later, she experienced relapses of a milder and transitory nature, though not involving the optic nerve system. These relapses were preceded by or coincided with a relatively low phase. This phase was illustrated by a slightly steadier curve. The "liberation" of blood platelets observed next caused the curve to rise and run a more fluctuating course. The fluctuations were not great, however. The blood platelet conditions during menses were rather interesting. The low level of the curve comprised two menstrual periods, while three fell at a higher level. The conditions, thus, were similar to those in Group 2.

Case 45.—Severe diffuse disseminated sclerosis. A definite parallelism was seen between exacerbation of the disease and a falling tendency of the blood platelet curve, and between improvement and a rise of the curve. In the phase corresponding to the last section of the curve the patient developed symptoms of polyarthritis, with increased S. R. and a temperature rise. The rheumatic symptoms developed during a period with a rather high blood platelet level. Within this period the patient experienced no exacerbation of neurological origin (Charts 12 and 13).

Case 70.—Patient admitted with symptoms of bilateral retrobulbar neuritis. The symptoms in one eye had started five weeks, and in the other a few days, before admission. On admission the blood platelet level was high, with two spontaneous agglutinations. A sudden aggravation of the symptoms in this eye occurred in about 10 days, and simultaneously the curve showed a pronounced falling tendency, with change of level of 250,000 thrombocytes. The level then rose again to the initial value, and the patient's condition improved, though slowly. During this period a mild leucocytosis was present. S. R. and temperature normal.

This curve showed only a lowering of the level during renewed activity, but no reactive rise. It was interesting to see that the lowering of the level lagged somewhat behind the exacerbation. It gave a "secondary" impression, but the whole level was rather high.

Case 96.—Neuromyelitis optica. Plotting of the blood platelet curve was begun during improvement of the eye symptoms (Charts 14 and 15), but the myelitic attack then came on, and the level fell, significantly, parallel with the exacerbation. On the following rise the activity had ceased. This section of the curve seems to represent the reactive phase of the myelitic attack, and the high initial level, the reactive phase of the optic nerve symptoms. Another period of light clinical activity was observed, followed by improvement, with a new reactive phase.

Case 20.—The patient was admitted 12 days after the onset of a myelitic attack, which was improving on admission. On the sixth day after his admission he experienced acute exacerbation of the myelitic attack, which coincided with a deep negative spike of 500,000 (Curve 16). Then followed a reactive rise simultaneously with improvement. The reactive rise lasted about 10 days.

The curves in Group 3 thus illustrate the same conditions as in Group 2. The most constant features are the reactive rises during improvement, against a low level during exacerbation. The curves are often evener at the low level; i. e., the fluctuations are smaller than during the reactive phases. Only in Case 70 was no reactive rise recorded, but there was a significant fall during clinical exacerbation. The level of the first half of the curve was here slightly higher, if anything, than that of the second half. This relatively high initial level possibly represents a reactive rise after the first grave symptoms, with which fresh symptoms overlapped. But the reactive rise that should follow the last attack is missing. The patient's loss of vision persisted for some months.

An attack may thus very well come on with a high blood platelet level, which is afterward "depressed" coincidentally with progression of the fresh symptoms. The absolute blood platelet number, therefore, is of no definite significance. The average number was the same for the acute and the stationary cases

and fell within the range of the normal values found by Heinild.

PHENOMENON OF AGGLUTINATION

One of the advantages of Heinild's technique is the elimination of the well-known tendency of the blood platelets to extravascular spontaneous agglutination. This was obtained by pipetting with acetic acid. Even this procedure is occasionally insufficient. It is strange that spontaneous agglutinations in the counting chamber were seen far more frequently in the sclerosis series than in the control series (Table 4).

TABLE 4.—*Frequencies of Agglutinations During Thrombocyte Counts Compared for Active and Inactive Disseminated Sclerosis Patients as Well as for Controls and Inactive Disseminated Sclerosis Patients*

	Active Sclerosis	Inactive Sclerosis	Total Disseminated Sclerosis
Agglutination	65	48	113
No agglutination	870	2,170	3,040
Total	935	2,218	3,153
	Normals + Controls	Inactive Sclerosis	Total
Agglutination	2	48	50
No agglutination	789	2,170	2,959
Total	791	2,218	3,009

The frequencies of spontaneous agglutinations in the counting chamber have been compared for patients with active and patients with inactive disseminated sclerosis, as well as for normals plus controls and patients with inactive sclerosis. It appears from the analysis that when the patients with active sclerosis showed more agglutinations than the patients with inactive sclerosis (χ^2=43.63; $P<0.1\%$), and these, again, more agglutinations than the normals and controls, the difference could hardly be due to accidental variation of the observations (χ^2=13.03; $P<0.1\%$).

Chart 17 throws further light on the problem. The patient had progressive disseminated sclerosis and the blood showed spontaneous agglutinations every day. To make sure, we made double punctures, i. e., puncture of the right and left cubital veins simultaneously. The agglutinations continued during the bishydroxycoumarin (Dicumarol) treatment, until the prothrombin per cent began to fall. The platelets were then detached, only to become agglutinated again with rising prothrombin concentration. This reaction was reproducible. The question of the influence of bishydroxycoumarin treatment on the blood platelet level will not be further discussed in this paper. Reference may be made to a previous statement in the reports of the International Congress for Neurologists in Paris, 1949.[11] No significant difference was found between the variations in the blood platelet count with and that without bishydroxycoumarin treatment.

COMMENT

It appears from the present series that blood platelet counts for peripheral blood show greater variations in patients with disseminated sclerosis than in normals, and that these fluctuations are greatest in patients with the active disease. Clinically ascertainable activity over a short period is accompanied by a blood platelet depression, which during improvement is followed by a reactive rise. During the acute attack the blood platelet system thus reacts in principle as during an infectious disease. But we cannot simply conclude from this that an infection is present in these cases.

The usual criteria of acute infection are generally absent in disseminated sclerosis. We can, it is true, demonstrate changes in the leucocyte number (Hansen and Munch-Petersen [12] and Adamson and Støretebecker,[13] among others), as well as a shift to the left in Arneth's blood picture. Likewise, the S. R. and the temperature may in some instances be raised. These changes are, however, generally small and vague, by no means equaling those taking place in the blood system during an acute infectious disease. In a number of cases such changes do not occur at all, or at least one or more of the symptoms of the total syndrome of acute infection are lacking. The blood platelet fluctuations are in many cases comparable to the fluctuations seen during acute infections. The correlation demonstrated by Frey for sedimentation rate,

fibrinogen increase, lymphocytosis, eosinophilia, and blood platelet variations (Heinild [9]) is hardly present in disseminated sclerosis. Further investigations into this question should, however, be made before conclusions can be drawn. Persson [14] found increased fibrinogen values without rise of the sedimentation rate in his series of disseminated sclerosis patients.

Changes of the blood platelet level have been seen in conditions other than acute infection. Wright [10] observed a significant rise in the total number of thrombocytes about 10 days after an operation and demonstrated a close relationship between the degree of the rise and the amount of tissue destroyed. Parallel with the rise, she found an increased tendency to agglutination. This tendency often persisted beyond the 14 days that the reactive rise generally lasts (see Chart 4, for instance). The reactive rise can thus be regarded as the response of the organism to destruction of tissue. But other forces seem to be active as well, since in disseminated sclerosis the rise is first seen when the patient is improving clinically. The "consumption" of blood platelets may therefore very well be conceived to be abnormally great in an active phase. Not until the activity in the affected organ has ceased are blood platelets liberated from the already activated blood platelet system.

A drastic fall in the blood platelet number is seen in experimental shock, for instance, no matter whether it is an allergic or a peptone shock. A number of interesting investigations into the blood platelet conditions during shock have been published within recent years. The various writers seem to agree that the blood platelet fall holds a central position among the hematological changes in shock,‡ whereas there is some disagreement as to the importance that may be attached to this phenomenon. Heinild, on the basis of the literature, as well as his own studies, holds that the blood platelet fall in shock is secondary to and produced by a primary endothelial lesion. This question will not be further discussed here.

‡ References 15 through 19.

There can be hardly any doubt that the variations in the number of circulating blood platelets seen in disseminated sclerosis represent a general reaction of the organism occurring at a certain frequency and apparently causing changes exceeding those otherwise demonstrable in the organism during this disease. This is, of course, of particular interest in the case of a disease which in other respects bears a close relation to the vascular system.

SUMMARY

In disseminated sclerosis the permanent changes are localized along the blood vessels, being associated with venules and veins. Histological examination of fresh foci do not reveal serious thrombotic changes, but often clots of blood platelets are seen in the central veins. In the present work the blood platelets in the circulating blood were examined with a view to variations in their number. The blood analyses were as far as possible extended over a fairly long period, as a rule up to one month, and in a single case six months. The values obtained were compared with corresponding values from a control and a normal series. In "stationary" disseminated sclerosis we found moderate fluctuations of the blood platelet number, somewhat greater than in the normal and the control series. During clinical activity there was a tendency to a low level, followed by a rise during improvement. The fluctuations proved to be considerably greater in patients with acute disseminated sclerosis than in patients with the stationary form or in normals, or in patients with other neurological disorders.

In principle, the curves run a similar course during infectious diseases and after tissue destruction, operations, etc. An increased tendency to agglutination is possibly also reflected in the blood platelet system.

The counts showed, furthermore, that in normals the variations in blood platelet number are much greater from subject to subject than from day to day in one subject.

Though the series under review does not allow of a simple comparison between the individual variations of the thrombocyte

counts in patients with active and in patients with inactive disseminated sclerosis, the tendency toward a greater variability in the active group is so conspicuous that this question merits more thorough investigation.

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Cerebral Pathology Following Serum Anaphylaxis

L. S. MERIWETHER, M.D., New Orleans
H. HAGER, Dr. rer. nat.
and
W. SCHOLZ, M.D., Munich

The serious sequelae of serum therapy or prophylaxis in a person who has become sensitized either by previous serum injection or by contact with the animal type are well known to all physicians through the tragic consequences of anaphylactic reactions, in which death may follow within a few minutes or a few hours the injection of serum. The delayed reactions, such as urticaria, which occur several days after the serum injections, are also familiar.

The case we wish to present is unique in that the patient's life was spared in the early anaphylactic reaction; he lived to have the delayed reaction and to reveal symptoms of destructive central nervous system pathology. We know of no comparable case in our experience or in the literature, and we therefore present it from this standpoint. The final observation during his illness was made in Children's Hospital, and the postmortem examination was performed in the Pathological Institute of the University of Munich. The brain was sent to the Max-Planck-Insitut for investigation. The other pathological findings were given us in a protocol by the pathologist who conducted the autopsy. Our interest is confined to the pathological study of the brain and the correlation of our findings with the clinical course.

Ochsner Clinic, Department of Internal Medicine, New Orleans (Dr. Meriwether).

From the Department of Neuropathology of the Deutsche Forschungsanstalt für Psychiatrie, Max-Planck-Institut.

REPORT OF A CASE

J. L. (F. A. Nr. 142/50).

The patient was a boy 7 years old, the oldest child in the family. At birth the delivery was normal. Some retardation of body development in the earlier period of life was apparently overcome. At the age of one year he was given diphtheria serum because of suspected diphtheria. At the age of 3 years he developed diphtheria, and again he was given serum therapy. It was stated that he developed serum sickness after this treatment. There was no mention as to whether the reaction was an acute anaphylactic or a delayed urticarial one. At the age of 3 years a diagnosis of measles was made; there was no history of any complication or residual infirmity.

On May 11, 1950, at the age of 7, he had a cough and was said to be hoarse. The family physician was called in and gave him an injection of 16,000 units of bovine serum to prevent diphtheria. One and a half hours following the serum injection the patient became cyanotic; he was groaning, and the eyes were fixed in a vertical stare. His heart action was stated to be poor. The mouth was tightly closed. A state of asphyxia, thought to be on the basis of glottic edema, developed, and an emergency intubation was performed. He was transferred in haste to the local city hospital. During transportation it was necessary to keep the intubation tube in place to prevent suffocation.

On his arrival at the local city hospital, his general condition was described as very poor. He was pale; the lips were cyanotic and the extremities cold. On removal of the tube he was noted to have an inspiration stridor. The pulse was rapid. There were bronchial rales and stridor on respiration. No neurological symptoms or signs were noted at this time. He was given emergency supportive remedies. His condition was said to improve. The hoarseness disappeared, and he appeared to be sleeping more normally.

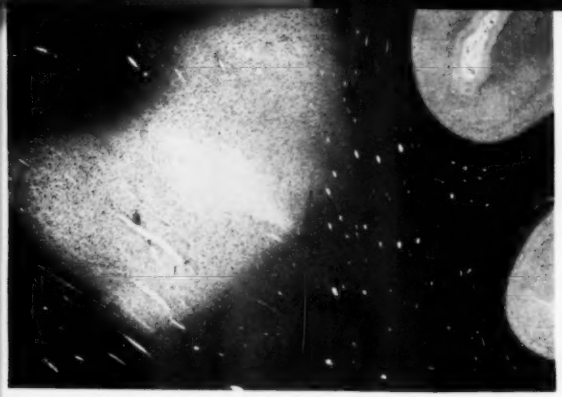


Fig. 1.—Occipital lobe. Area of demyelination in the white matter, fading toward the surrounding tissue. The central part shows liquefaction. The scattered black points are artifacts. Van Gieson stain.

On the following day his condition was greatly improved. He was happy and appeared to be making a good recovery.

Approximately three days after administration of the serum, he showed signs of rapid deterioration. He became incontinent of urine and feces. At midday choreoathetoid movements of his arms and legs were observed. There was grimacing of the face and grinding of the teeth. On the following day he was unable to speak, but the choreoathetoid movements were not as pronounced, possibly because of the medication, consisting of small doses of phenobarbital and 0.3 gm. of aminopyrine (Pyramidon) three times daily.

Approximately one day after onset of neurological symptoms a generalized urticaria developed, for which he was given an antihistamine. The choreoathetoid movements persisted, and the mother stated that on one occasion the child had a convulsion. The occurrence of the convulsion was not confirmed by a physician, although the child was in a hospital. It is possible that the mother could have mistaken active choreoathetoid movements for a true convulsion. The child became stuporous. Temperature 38 C. He was at that time transferred to the Children's Hospital of the University in Munich.

On observation at the time of his arrival, he was found to be stuporous, but he would respond slowly when spoken to. There were incoordinated athetoid movements. The fundi and the x-ray of his skull were normal. General physical examination revealed no other significant findings at that time. Laboratory studies, consisting of blood count, urinalysis, and spinal fluid studies, were normal.

The child's condition gradually deteriorated. In the latter part of the course it was stated that he lay in a "catatonic-like" position in his bed. There was a pronounced tremor of his tongue. Occasionally he cried spontaneously. His reactions were slow when he was spoken to. Leucocytosis developed, with a count of 17,400. Chlortetracycline (Aureomycin) and other supportive medication were administered.

During the last days of his illness he developed a flexion contraction of his legs and an equivocal Babinski sign; there was a tonic contraction of the left arm, and the right arm was flaccid. His response to speech was equivocal; he was unable to talk. He had a severe cough and respiration difficulties, which had existed since the early days of his illness.

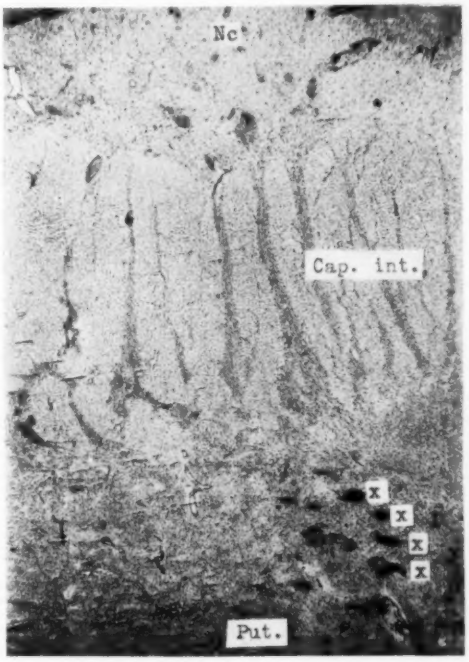
On the 21st day of his illness he became hyperpyretic, and all therapy was to no avail; he died on the following day.

Postmortem Examination.—The heart revealed a residual earlier mitral endocarditis. The lungs were acutely emphysematous; a hemorrhagic infarct was found in the left lower lobe. Petechial hemorrhages were observed on the pleural surfaces of both lungs. The bronchial mucosa appeared acutely inflamed.

On microscopic examination, the liver was found to have severe fatty degeneration in the central area of the lobules. The nuclei of the parenchymal cells appeared swollen.

Brain: Macroscopic examination. The formalin-fixed brain was received intact. It weighed 1480 gm.

Fig. 2.—Almost complete loss of nerve cells within the caudate nucleus (*Nc*) and the putamen (*Put*) with correspondingly diffuse glial proliferation. The myelin fiber tracts are replaced by linearly arranged fat granule cells (*x*). *Cap. int.* indicates the internal capsule. Nissl stain.



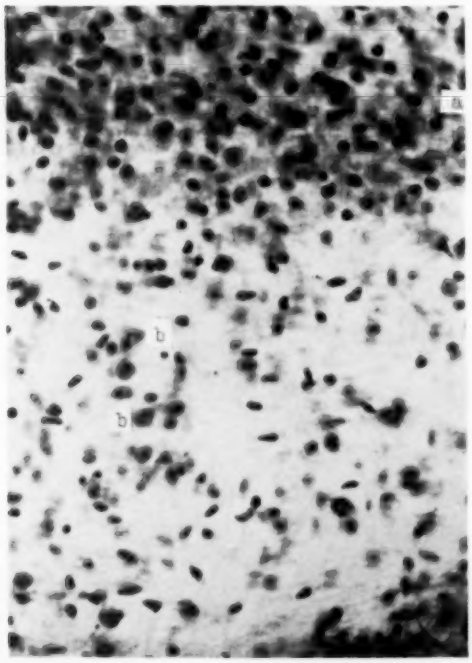
The meninges, basal vessels, and external configuration of the brain appeared normal.

Section of the brain revealed a diffuse homogeneous appearance of the white matter of the parieto-occipital region, becoming increasingly pronounced as the occipital lobes were approached. In the left occipital lobe was a pea-sized area of complete myelin destruction with liquefaction. There were no visible changes in character or consistency in other areas of the cerebrum, cerebellum, or brain stem.

Microscopic examination. Within the central part of the white matter of the occipital lobe, corresponding to the area of liquefaction mentioned, there was a rather sharply demarcated region with almost complete destruction of the myelin fibers, and here the glial nuclei had lost their ability to stain (Fig. 1). In the region surrounding the area of complete destruction and liquefaction, no distinct reaction of the glial tissue was seen. No evidence of fatty metamorphosis was present. The vessel walls in this area appeared edematous, and there was complete absence of mesenchymal reaction. The process was one of edematous necrosis and liquefaction. In the neighboring cortex, in contrast to the white matter, there were only minimal signs of mild, diffuse edema. The myelin fibers in the cortex revealed areas of swelling of varying intensity. There was no distinctly visible alteration of the nerve cells in any portion of the cortex.

The most impressive pathology was seen in the basal ganglia. The Nissl stain revealed that almost the entire striatum was involved, with complete loss of the nerve cells and a diffuse glial reaction;

Fig. 3.—Higher magnification of area in Figure 2, showing conditions within the striatum: (*a*) accumulation of fat granule cells within the territory of a myelin fiber tract; (*b*) ischemic nerve cells, diffuse microglia and macroglia proliferation. Nissl stain.



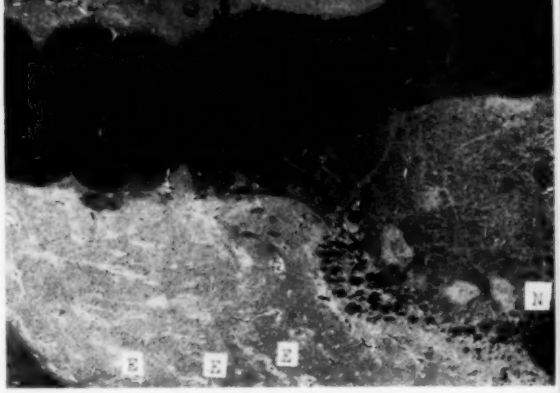


Fig. 4.—Multiple appearance of perivascular edema (*E*) in the striatum; pea-shaped areas of necrosis (*N*) within the external part of the globus pallidus. Van Gieson stain.

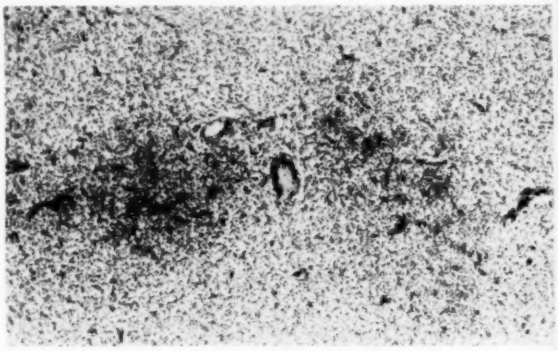


Fig. 5.—Two areas of necrosis in the globus pallidus filled with granular cells and showing distinct reparative vascular reaction. Nissl stain.

Fig. 6.—Paling of Sommer's sector (*x*–*x*) in the cornu Ammonis, with beginning of slight microglia and vascular reaction.

the myelin fiber tracts passing through this nucleus were outlined by fat granule cells linearly arranged along their course (Figs. 2 and 3). A slight reaction of the cells of the vessel walls was to be seen in a few scattered areas only. These morphologic changes were confined to the striatum except in that portion adjacent to the globus pallidus, in which there was not the same high degree of generalized neuronal necrosis. In the striatum the remaining nerve cells presented the picture of ischemic changes, as described by Spielmeyer. Within the external section of the globus pallidus, pea-shaped areas of softening of the tissue were visible (Fig. 4). These were filled with fat granule cells, and a distinct reparative reaction of the vessels was evident (Fig. 5).

In the cornu Ammonis we observed the picture of paling of Sommer's sector. All nerve cells had disappeared, and a diffuse proliferation of rod cells was found within the entire field (Fig. 6). Here, also, the vessels revealed a slight progressive reaction, whereas the macroglia cells were not yet increased in number. Apparently, here the intensity of the necrotizing process bordered on softening of the tissue.

Van Gieson preparations gave further evidence of the pathogenesis of the process. They demonstrated circumscribed perivascular areas of edema in the basal ganglia with severe myelin destruction (Fig. 4).

The intensity of the necrotizing process varied from place to place within the involved parts of the basal ganglia. The morphological changes were diffusely distributed through the striatum, whereas in the globus pallidus the tissue was generally better preserved except for the areas of softening mentioned. There were a few small focal lesions of the same character and intensity noted in the subthalamic region.

The olivary nucleus, the dentate nucleus, and the cortex of the cerebellum revealed no evidence of a pathological process.

COMMENT

Since Gangolphe and Gardère reported a case of serum neuritis in 1908, observations of damage to the peripheral nervous system in serum disease have increased in Thaon,[28] 1912; Lhermitte and Haguenau,[17] 1937; Verger, Aubertin, and Delmas-Marsalet,[30] 1927; Taillos, 1936; Schipkowensky,[25] 1937; Sprockhoff and Ansorge,[27] 1938; Bennett, 1939; Elsässer,[5] 1942, and Hughes,[11] 1944.

Complications in the central nervous system are not frequent. Park and Richardson [20] (1953) recently compiled a list of such cases. These complications are chiefly general cerebral signs and the development of paretic symptoms, often of a hemiparetic character. An increase in pressure, cell number, and protein content of the spinal fluid was also present in some cases (de la Vergue, Bannwarth, and Abel). Occasionally symptoms, such as meningismus, somnolence, coma, and epileptic fits, were observed. Such cases were published by Morichau-Beauchant [19] (1923); Foster-Kennedy [13] (1929); Bourgignon [2] (1931); Charleux [3] (1932); Tzank, Schiff, and Abadi [29] (1935); Gautier and Seidemann [8] (1935); Roger and Paillas [22] (1936); Ledoux, Desruelles, and Gomet [15] (1937); Kroll [14] (1938); Lemièrre, Laporte, and Domart [16] (1938); Michon and Heully [18] (1946); Fisher [6] (1949); Hausmann [10] (1952), and Park and Richardson [20] (1953). These complications in the central nervous system are not often fatal, and pathological observations are therefore rare. As far as we know, there exist only two papers on pathological findings in the central nervous system. Roger, Poursines, and Recordier [23] (1934) reported a patient who 18 days after antitetanus serum therapy for 26 days developed generalized polyneuritis and died some three weeks later. In the postmortem examination the following changes were observed: in the brain, hemorrhagic meningeal exudate, dilated pial vessels, interstitial edema of the cortex; in the spinal cord, dilatation of the small meningeal arteries and limited hemorrhages, and small areas of necrosis. Winkelman and Gotten [32] (1935) described another case of serum sickness. Two days after injection of horse serum the patient developed serum disease. After an interval of 19 days marked cerebral symptoms arose. The connection between serum disease and symptoms of the central nervous system are not certain in this case. The pathological findings refer mainly to the spinal cord; marked meningeal infiltration distention of the anterior horn cells and perivascular infiltrations

in the white matter, with many glial foci, were noted. Similar patches were found in the brain, with numerous areas of necrosis and accumulation of gitter cells.

These findings correspond closely with those reported by Garcin and Bertrand [7] (1935) following repeated anaphylactic shock in animals.

In the analysis of our case, we feel that it is more intelligible to consider the pathological alterations of the tissue and their pathogenesis in correlation with the symptomatology as revealed in the patient's clinical course.

The most evident macroscopic alteration was the edema; the most profound edematous process was in the occipital lobes. In this region microscopic study revealed diffuse myelin destruction, as has previously been reported in severe edema by Anton,[1] Greenfield,[9] Jacob,[12] and Scheinker.[24] In such conditions one frequently sees myelin destruction in the white matter with minimal interstitial reaction; often, all components of tissue are liquefied without any reaction.

In the gray matter, Scholz [26] pointed out that the nerve cells in the cortex and elsewhere are rather resistant to a pure type of edema without complicating hemodynamic anoxia. In the case reported the cortex was well preserved.

The pathological findings in the striatum and globus pallidus were more complex. Here we observed myelin destruction in various manifestations, namely, perivascular, corresponding to the perivascular edema, and distributed more diffusely throughout the striatum, especially observed in the destruction of most of the myelin fiber tracts passing through this nucleus. In addition, there was evident nerve cell necrosis of the ischemic type, seen especially in the striatum. This signifies a necrotizing process with the intensity of a selective neuronal necrosis, caused by anoxia due either to hypoxemia or to temporary oligemia. The selective involvement of the basal ganglia suggests hypoxemia as an essential pathogenetic factor, as stated by Scholz. He pointed out that hypoxemia of a certain degree of intensity regularly produces vasomotor reactions, which, in turn, complicate the morphologic picture of pure hypoxemia by focal lesions. Such a pattern of focal lesions in the pallidum is best demonstrated in carbon monoxide poisoning. The same process is evidenced by the symmetrical focal softenings within the pallidum in our case. The typical localization of the lesion in the cornu Ammonis is further evidence of the importance of localized functional vascular disturbances in the hypoxemic pathogenesis of these lesions. The topistic character and distribution of these lesions are further evidence of their hypoxemic pathogenesis.

From the morphologic pathology, we conclude that two conditions were effective in the production of the brain changes in this case:

1. Hypoxemic anoxia of the brain, producing the changes of topistic character in the basal ganglia
2. A condition producing the generalized edema, of varying intensity, with destruction of myelin structures

In considering the symptoms in the course of this patient's illness, we find that just prior to the onset of significant symptoms an injection of serum was given to an already sensitized patient, with resulting severe anaphylactic shock and the complicating laryngospasm or glottic edema, more probably the latter. The glottic edema produced severe asphyxia at the onset, and it persisted in a milder degree throughout the course of the illness. A delayed anaphylactic reaction was manifested by an urticarial reaction a few days later.

It is known that anaphylaxis causes increased permeability of vessels in organs or tissues of the body other than the brain; this case reveals that it can also produce severe edema in the brain. Hypoxemia with anoxia due to asphyxia was the complicating factor in this case. The degree and duration of asphyxia were obviously severe. Perhaps neither the increased vascular permeability

of anaphylaxis nor the hypoxemia of the asphyxia would have been sufficient in itself to have produced its characteristic morphologic tissue alteration; but, working in symbiosis, one assisted the other in producing the severe changes, which showed their individual characteristics.

SUMMARY

A previously sensitized patient was given serum, with resulting acute anaphylaxis, which he survived, and a few days later developed symptoms of delayed anaphylaxis, as manifested by urticaria. Psychic and neurological symptoms, with extrapyramidal features, developed in conjunction with the delayed serum reaction.

The pathological findings in the central nervous system are described, and their pathogenesis is analyzed from the standpoint of morphologic pathology. The pathogenic factors of edema and hypoxemia correlate with those derived from clinical symptoms of anaphylaxis and asphyxia during the course of the patient's illness.

From a clinical standpoint, this case serves as a warning of the multiple difficulties to be encountered by indiscriminant serum prophylaxis in treatment of persons who may be sensitive to the particular serum.

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Kernicterus

Hypoxemia, Significant Pathogenic Factor

L. S. MERIWETHER, M.D., New Orleans
H. HAGER, Dr. rer. nat.
and
W. SCHOLZ, M.D., Munich

The term "kernicterus" was coined by Schmorl,[1] who in 1903 reported observations of bile staining in the basal ganglia, cerebellum, and brain stem in the newborn infant with jaundice, similar to those recorded by Orth [2] in 1875. In 1932 Diamond, Blackfan, and Baty [3] considered anemia, hydrops fœtalis, and icterus gravis to be manifestations of erythroblastosis fœtalis. Eight years later Landsteiner and Wiener [4] discovered the Rh factor in human blood. The following year Levine and associates [5] explained most cases of erythroblastosis fœtalis on the basis of isoimmunization of the mother by the Rh antigen of the fetus; the antibody being formed in the mother passes through the placenta to the fetus, with resulting destruction of erythrocytes. In 1946 Wiener * pointed out that there were other factors necessary to explain all cases of erythroblastosis and made note of other antigen-antibody substances to explain those cases which would otherwise be unexplained on the basis of an Rh factor.

To explain why hydrops develops in some infants with erythroblastosis and icterus gravis neonatorum in others, Wiener stated that there are two types of hemolytic disease of the newborn: congenital hemolytic disease and icterus gravis neonatorum, the form being in his opinion dependent on the form of the maternal antibody. According to him, the univalent, or incomplete, form may pass through the placenta and become attached to the fetal erythrocytes, causing progressive anemia and hydrops of the fetus. In mothers whose antibody has a low titer, the infant may be born alive but anemic. Such infants usually survive with the aid of transfusions. Wiener stated that icterus gravis is caused by an agglutination form of maternal antibody which is unable to pass through the placenta while in situ but does so during the trauma of separation at the time of birth, causing agglutination in vivo of the erythrocytes of the newborn, which may result in kernicterus. He considered the final stage in the development of kernicterus to be due to agglutination of cells in the capillaries of the brain, with resulting anoxia. Many investigators in this field are not in accord with the theories of Wiener. Pickles,[9] who has more recently reviewed the literature, considers the hemolysis to be "a reaction to the sensitization which is dependent on the time that the foetus has been subjected to the action of the immune agglutinins, on its capacity for hemolysis and on its ability to excrete these products after birth." Finally, all theories consider the severe anemia to be due to hemolysis. Consequently, any theory which admits hemolysis must admit anemia.

In reviewing the literature, we have been impressed by the consistency of findings in the pathologic reports on kernicterus in persons dying in the acute phase. We have been equally impressed by the inconsistency in the theories of the pathogenesis of kernicterus.

As Pentschew [10] emphasized, this condition, which he designated as "encephalopathia posticterica infantum," assumes even greater significance when it is realized that a large

Ochsner Clinic, Department of Internal Medicine, New Orleans (Dr. Meriwether).

From the Department of Neuropathology of the Deutsche Forschungsanstalt für Psychiatrie, Max-Planck-Institut.

* References 6 through 8.

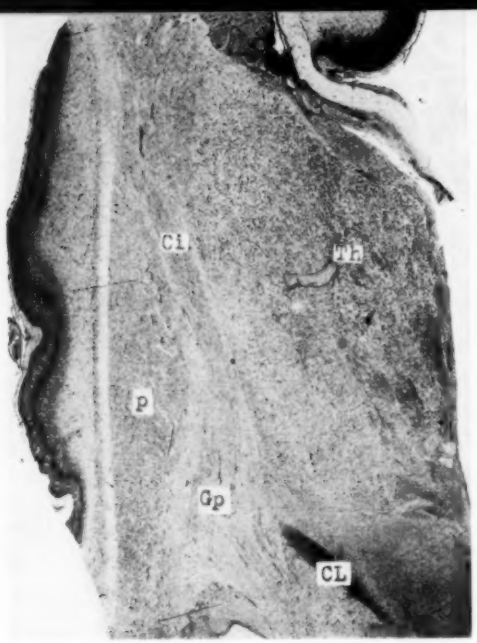
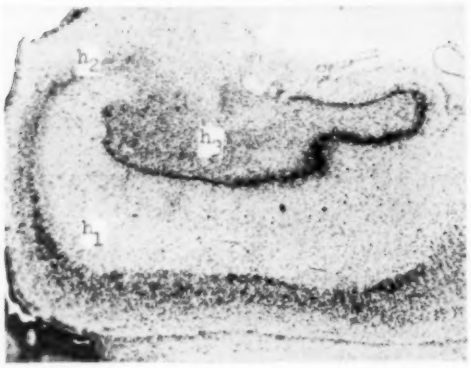
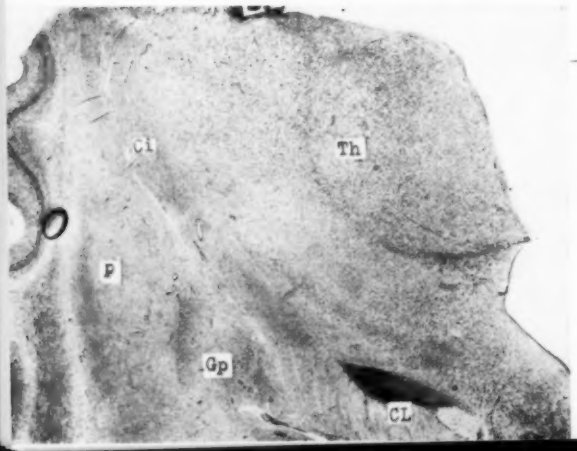


Fig. 1 (Case 1).—Frontal section through the basal ganglia. Topistic absence of nerve cells and glial proliferation in globus pallidus and corpus Luysi. In this Figure, and in the accompanying Figures, *p* indicates putamen; *Gp*, globus pallidus; *CL*, corpus Luysi; *Th*, thalamus; *Ci*, capsula interna. Nissl stain.

Fig. 2 (Case 1).—Loss of nerve cells and corresponding glial proliferation in Field h_3 of the cornu Ammonis. Considerable rarefaction in Field h_2 and partly in Field h_1. Nissl stain.





percentage of the infants with erythroblastosis who survive the acute phase have residual symptoms referable to the central nervous system. The number of such patients may comprise a greater percentage of those handicapped by extrapyramidal symptoms.

Little, if any, significance has been given to these residual symptoms and pathologic observations from the pathogenic standpoint. We believe that the pathologic changes in such cases are of extreme importance in the interpretation of the pathogenesis, in view of our present knowledge of the specific reactions of the elements of the cerebral parenchyma. Accordingly, two representative cases which show the pertinent residual pathologic changes will be presented and their pathogenic significance will be discussed.

REPORT OF CASES

Case 1.—W. M. (F. A. 76/43), a male infant, was icteric from the first day after birth. Rapidly progressive anemia with increasing jaundice was noted from two to four days after birth, during which time opisthotonos and extreme hypertonicity of the muscular system, more pronounced in the lower extremities, developed. These neurologic symptoms persisted. The patient remained in the hospital during his entire life, dying at the age of 3½ weeks of pneumonia. The diagnosis was icterus gravis.

Macroscopic Observations.—The formalin-fixed brain weighed 450 gm. The meninges and basal vessels appeared normal. The configuration and external surface of the brain showed no abnormality. On section, the white matter of the cerebrum had a light grayish appearance, as is usual in immature myelination. The border between the cortex and the myelinated zone was not distinct. No discoloration or other gross pathologic changes were noted in the region of the basal ganglia.

Microscopic Observations.—Myelination and cortical development were considered to be normal for the patient's age. The most impressive observation was the symmetrical and almost total absence of nerve cells, with profuse glial cell proliferation, in

Fig. 3 (Case 2).—Frontal section through the left basal ganglia. Topistic loss of nerve cells and corresponding gliosis within the globus pallidus and the corpus Luysi. Focal change of the same character in the lateral region of the putamen and diminution of the nerve cells within the ventral region of the lateral nucleus of the thalamus; the same focal change within the medial nucleus (see Fig. 4). Nissl stain.

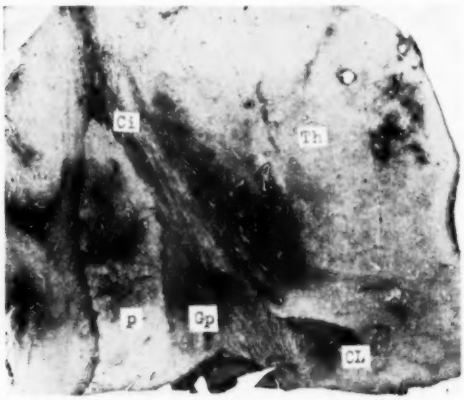
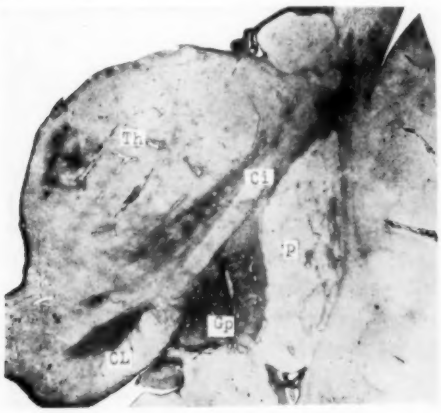


Fig. 4 (Case 2).—Preparation, from the same region as Figure 3, demonstrating the distribution of the lesions mentioned in Figure 3 by the development of a dense fibrous gliosis. Holzer stain.

the globus pallidus and in the subthalamic corpus Luysi (Fig. 1). Such a localized process is described by the German investigators as *topistische Erkrankung,* or *systematischer Nervenzellausfall.* The cornu Ammonis revealed absence of cells in the endplate (h_3) and reduction of the granular layer, corresponding to glial proliferation (Fig. 2). The resistant part (Field h_2) and Sommer's sector (h_1) were involved, too, the latter only partly (Fig. 2).

In the cerebellum, extreme decrease in number of the neurons within the dorsal area of the dentate nuclei was noted; some reduction of the myelin fibers was also present. The changes in the dentate nuclei and cornu Ammonis were symmetrical, as in the basal ganglia. The cerebellum appeared otherwise normal; the Purkinje cells were well

Fig. 5 (Case 2).—Frontal section through the right basal ganglia, demonstrating the symmetry of the lesions in the basal ganglia, globus pallidus, and corpus Luysi, with an especially dense topistic glial fibrosis. Holzer stain.



preserved. No distinct evidence of disease was observed in the striatum, the thalamus, or any other part of the brain, including the medulla oblongata.

Case 2.—W. R. (F. A. 49/43), a male infant, had icterus gravis within the first few days of life. On admission to the hospital the patient was extremely icteric and anemic. Severe spastic tetraplegia developed. The liver was enlarged. No notation was made of the spleen. The jaundice diminished, but the neurological symptoms persisted and the patient showed evidence of a psychic disturbance. He died at 5½ months of age of an intercurrent disease.

Macroscopic Observations.—The formalin-fixed brain weighed 510 gm. The meninges, basal vessels, and external configuration of the brain appeared normal. On section of the brain, the cornu Ammonis showed symmetrical increased consistency to palpation and was distinctly smaller than normal. There

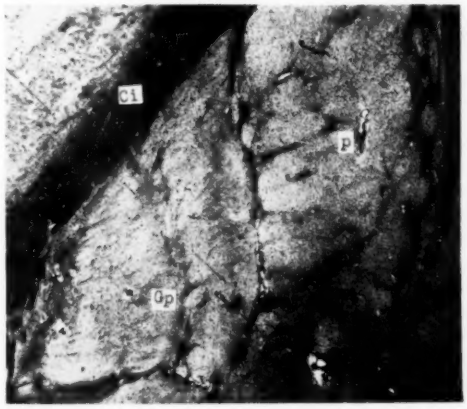


Fig. 6 (Case 2).—Section taken from the same block as Figure 5. A status marmoratus has developed in the lateral portion of the putamen. Demyelination of the globus pallidus. Heidenhain stain.

was some increase in consistency, also, in the region of the basal ganglia.

Microscopic Observations.—The Nissl preparation of the basal ganglia showed a most impressive complete absence of nerve cells in the globus pallidus and definite associated gliosis, with pronounced glial fibrosis, as seen in Holzer preparations (Figs. 3 to 5). There were no areas of softening or vascular proliferation. A similar symmetrical process was noted in the subthalamic corpora Luysi. The gliosis of the globus pallidus and corpora Luysi was sharply demarcated, without any involvement of the bordering tissue.

In the striatum were seen circumscribed focal areas of nerve cell loss and corresponding fibrous gliosis. These focal areas were more apparent in the lateral portion of the putamen, and in its extreme lateral portion they became confluent and appeared

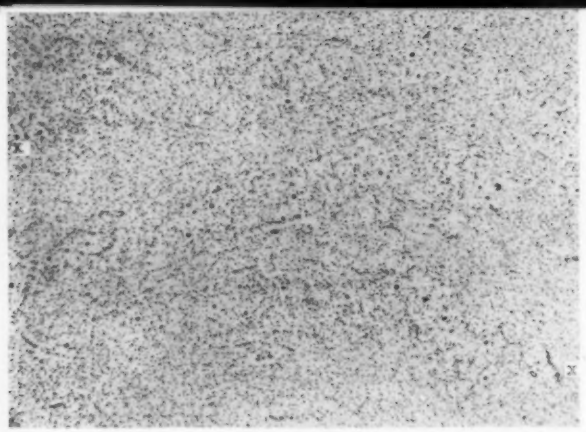


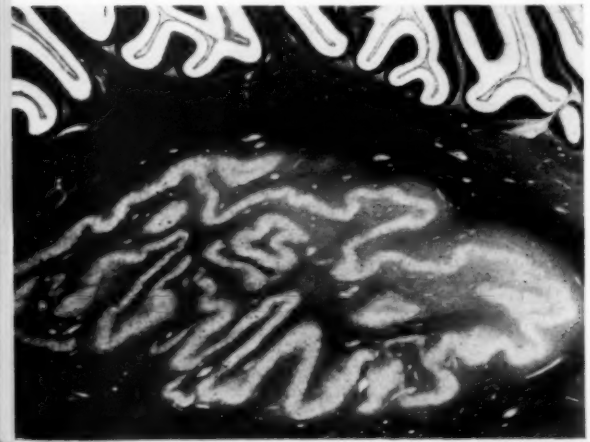
Fig. 7 (Case 2).—High-grade diminution of nerve cells in the dorsal part of the dentate nucleus, *x–x* marking the band of the dentate nucleus. Nissl stain.

as a single elongated area on the lateral border. In the region of the gliosis within the putamen, the myelin stain revealed the development of a real status marmoratus (Fig. 6). In the thalamus a few scattered areas of focal loss of neurons were observed in the medial nucleus and in the ventral part of the lateral nuclear groups. The mammillary bodies also showed a decrease of their neuron population. The cornu Ammonis, too, had participated, with loss of nerve cells; these changes involved the granular layer, end-plate, and Sommer's sector, and even of the resistant part only a small island of cells had remained. The absence of nerve cells was correlated with glial proliferation, as in the pallidum. In addition, the Sudan stain revealed that some fatty substances not resorbed had remained in this sclerotic area.

There was a slight decrease of a generalized character in the staining intensity of the myelin in the white matter of the cerebrum, and in the Holzer stain diffuse generalized minimal gliosis was observed.

In the cerebellar cortex an occasional *Strauchwerk* was observed, although the Purkinje cells appeared on the whole well preserved. The dentate nucleus, however, showed practically complete absence of nerve cells and demyelination, with associated gliosis in its dorsolateral area (Figs. 7 and 8).

Fig. 8 (Case 2).—Demyelination within the dorsolateral region of the dentate nucleus. Myelin stain.



Summary of Microscopic Observations in the Two Cases.—The significant changes in the two cases are practically identical. An almost complete loss of nerve cells with sharply demarcated gliosis was observed bilaterally in the globus pallidus, subthalamic corpus Luysi, and dorsal portion of the dentate nucleus. The destruction in the dentate nucleus was not as complete as it was in the globus pallidus and corpus Luysi, being more pronounced in the dorsal area. The lesions were symmetrical and pronounced in both cases. Other findings revealed residua of focal neuronal necrosis in the putamen and thalamus and corresponding changes of the mammillary bodies in one of the cases. Loss of nerve cells with gliosis in the cornu Ammonis was noted in both cases, which were atypical in that there was not such pronounced selectivity of a particular area as is usually characteristic of selective neuronal necrosis.

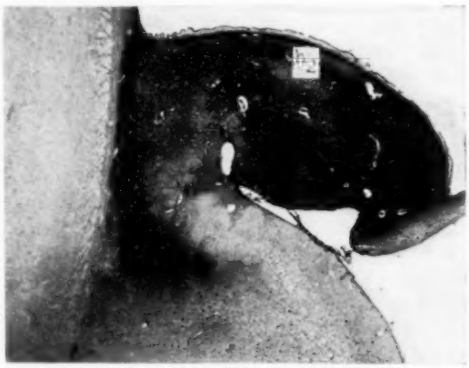


Fig. 9 (Case 2).—Total shrinking and fibrous gliosis of the cornu Ammonis. Only in Field h_2 is the gliosis less dense. Holzer stain.

COMMENT

In the past it has been difficult to explain the cerebral damage associated with icterus gravis. A large percentage of children having erythroblastosis complicated by icterus gravis have not survived the acute stage. Practically all cases thoroughly investigated in the past have been of such patients. In an attempt to explain the icteric discoloration of the involved nuclear areas, various the-

ories have been propounded, only a few of which will be mentioned here. The theory of infection has been rejected by the more recent investigations.

Wiener and Brody [11] explained the pathologic alterations in the central nervous system on the basis of an immunologic process, resulting in agglutination of erythrocytes with thrombosis of the small vessels to the particular areas. Such a process should give a picture of focal softenings diffusely spread throughout the brain. In the first place, however, we are dealing in our cases with a process of selective neuronal necrosis; secondly, this process has the pattern of topistic lesions in so far as the whole territory of special nuclei is involved, whereas the changes do not go beyond their limits. These findings could not be explained by the thrombosis theory.

Boorman and Dodd [12] and Dereymaeker [13] considered the pathologic process in the central nervous system to be a local antigen-antibody reaction in the tissues. Dereymaeker gave newly born kittens serum from rabbits which had been immunized with cat's blood; examination of the central nervous system revealed pathologic changes which were not characteristic of the selective ischemic cell changes in kernicterus of the newborn reported by Jacob.[14] With the anaphylactic factor of Dereymaeker, an increased permeability of the vessels with resulting edema should be expected. It cannot be denied that changes in the barrier function are present in the acute stage. But certainly they are not the intrinsic factor in the late changes. A nonhemodynamic edema affects many more myelinated structures than the ganglion cells, as has been demonstrated by Scholz.[15] Moreover, there is no explanation for the nuclear localization in Dereymaeker's theory.

The excellent contributions of Diamond and associates † have demonstrated the tragic, as well as the socioeconomic, importance of kernicterus. These investigators clearly showed the importance in the prevention of kernicterus of early exchange transfusions in patients with erythroblastosis. They also advocated administration of oxygen to patients with erythroblastosis, but they believed that oxygen administration is of minor importance. We concur in general with their opinions but do not believe that the bile pigment per se is important in the production of lesions in the brain in kernicterus. Patients with congenital atresia of the common bile duct do not exhibit the pathologic changes seen in the brain of patients with kernicterus. Diamond and co-workers showed that the pathogenic process of kernicterus is of only a few days' duration; consequently, it is important to recognize kernicterus early, so that exchange transfusions may be given in order to prevent the central pathologic changes.

Our investigations have convinced us that the pathologic changes in kernicterus can be explained on the basis of the residual pathologic findings in infants who have survived the acute process. From our investigation of the two cases herein reported, as well as from the observations of others, we are convinced that the entire process is the result of general anoxia of the brain resulting from hypoxemia. In the first place, histologic study in acute cases demonstrates that the nerve cell destruction is due to ischemic or hypoxic necrosis. The icteric staining may be a type of supravital process. By their "topistic" character, the residual alterations give the strongest and final link in the chain of proof of the pathogenesis of lesions in the central nervous system.

Rarely does one obtain a brain specimen whose structural alteration is due entirely to general anoxia by hypoxemia. Meyer [24] demonstrated that in animals with carbon monoxide poisoning the most intensive destruction is always in the globus pallidus. Meyer and Blume [25] showed selective lesions in the globus pallidus in 50% of cats in which narcosis was produced by administration of an ether-carbon dioxide mixture in order to produce asphyxia. Moreover, there have been numerous reports of symmetrical necrosis of the globus pallidus following carbon mon-

† References 16 through 23.

oxide poisoning in human beings. Abbott and Courville [26] observed symmetrical necrosis in the globus pallidus in cases of nitrous oxide narcosis without cardiac arrest. Many investigators ‡ have demonstrated that in man the globus pallidus is the area in the brain most vulnerable to secondary anemia. Titrud and Haymaker [32] reported three cases of delayed death due to decreased oxygen in high altitude flying. They found changes of a focal character in the striatum, pallidum, and Sommer's sector of the cornu Ammonis, similar to those produced by carbon monoxide poisoning in human beings and animals. In all these cases the pathogenic agent was intense and rapid in its action and produced focal lesions of a vascular character, but systemically located in vulnerable regions. The focal character of these lesions has been recognized by neuropathologists for many years. From the physiologist's standpoint, Opitz and Schneider,[33] Best and Taylor,[34] and McLeod [35] stated that hypoxemic anoxia above a certain degree always produces a vasomotor reaction of the vessels of the brain, resulting in oligemic areas and corresponding destruction. Investigations by Scholz and Schmidt [36] on experimental asphyxia in the brain of cats, using the Pickworth stain, revealed many such areas of localized ischemia distributed all over the brain, as well as in the pallidum. Therefore, as pointed out by Scholz [37] in a recent report, in cases of generalized oxygen deficiency in the brain one is confronted with two morbid agents: the generalized hypoxemic anoxia and the localized focal ischemia caused by secondary vasomotor reactions. If the localized ischemia occurs in a vulnerable area, such as the pallidum, corpus Luysi, dentate nucleus, or cornu Ammonis, which has been made more susceptible by a preceding hypoxemic anoxia, the ischemia will here show the first results of structural alterations, and elsewhere there will, at that time, be no obvious morphologic damage. The areas of morphologic change appear as vascular foci. In our investigation of the two cases reported here, the focal damage in the striatum, thalamus, and other nuclear areas, as well as the atypical pathologic changes in the cornu Ammonis, is evidence for such secondary vascular reactions as a pathogenic factor. Such morphologic changes are found in various modifications in cerebral oligemia. It is only in those cases in which vulnerable structures are partially or completely involved that the specific vulnerability of these units may become evident as true "topistic" alterations. Therefore, the most significant cases are those in which pure hypoxemia has existed for a sufficient length of time and is of such severity as to produce morphologic change in the given length of time, and not to the degree of causing a secondary vascular reaction with its additional consequent pathologic tissue changes. Scholz [38] reported such a significant case, that of a patient with a congenital cardiac lesion and chronic oxygen deficiency who lived 18 years. The effect of the chronic hypoxemia was evidenced in the brain by the reduction of the nerve cells in the globus pallidus, corpus Luysi, and dentate nucleus; the residual nerve cells in these areas were atrophic. A dense gliosis was present in the corresponding areas of the nuclear destruction. The pathologic changes were symmetrical and sharply demarcated. There were similar changes of less intensity in the striatum and the inferior olivary nucleus. The cortex of the cerebrum and cerebellum appeared normal.

In two other cases investigated by Scholz, but not reported, a similar combination of significant pathologic alterations was noted, in one of which there was a precipitate delivery with asphyxia, and in the other, delivery of the infant within an intact amnion. In the latter there was necessarily a period of profound hypoxemia, which persisted from the time of placental separation until the amnion was opened and the infant resuscitated. Both patients lived long enough that the anoxic changes, consisting of "topistic" lesions of the globus pallidus and corpus Luysi, were apparent.

‡ References 27 to 31.

Comparison of these and somewhat similar cases from the standpoint of clinical history and pathologic alterations in the central nervous system with cases of kernicterus makes apparent the fact that the characteristic and selective localization of the significant pathologic changes is the same in all. The typical order of morphologic alteration is based on the special vulnerability of the tissues, an idea which is the Vogts'[39] concept of "pathoclisis." In the cases of kernicterus the more focal loss of cells in the striatum, cornu Ammonis, and elsewhere, as observed in the cases reported here, is the result of an incidental vascular reaction similar to that observed in the more acute cases of hypoxemia. In addition, the circumscript changes are in many ways analogous to those observed in epilepsy, in which it is believed that a functional vascular disturbance is operating during and after seizure.[40] In the cases reported here, the absence of a history of convulsions is further evidence in support of the view that the hypoxemia alone was responsible for the "topistic" and focal pathologic changes.

The lesions in the cases reported here are such as would be expected from a mean average between two extremes, that is, somewhere between what is to be expected from hypoxemia of short duration and severe intensity, on the one hand, and, on the other, lower-grade intensity and long duration, such as is the case of congenital heart disease with hypoxemia.[38]

Richter[41] gave monkeys an inhalation mixture containing air and a small amount of carbon bisulfide over a period of many months. This produced distinct symmetrical lesions in the pallidum and substantia nigra. It was his opinion that the carbon bisulfide affected the enzymes of tissue respiration. His opinion in regard to enzymatic effect is identical with the concept of the action of cyanide poisoning experimentally demonstrated by Meyer.[42]

In accord with past experience, the finding of symmetrical total absence of nerve cells in the globus pallidus always is suggestive evidence of hypoxemia as the basic pathogenic factor. The combination of total cell loss and sharply demarcated gliosis in the globus pallidus, corpus Luysi, and dentate nucleus is convincing evidence. The other localized areas of destruction, as observed in the cornu Ammonis, thalamus, striatum, mammillary body, or elsewhere, are not sufficient within themselves to be of great value in the determination of hypoxemia, since they alone signify vascular reactions occurring also in many situations of pure oligemia.

There are certain unmistakable fundamental similarities between the two cases here reported and other cases, of known hypoxemia. Therefore, the deduction must be allowed that the brain tissue lesions in the cases reported are the direct and indirect effects of hypoxemia. There are no conditions except oxygen deficiency or impossibility of utilization of oxygen in which lesions of topistic patterns occur, and therefore there is no other way than by hypoxemia to explain the pathogenesis of such remarkably distinct and perfectly symmetrical lesions as are found in the cases reported. In view of these considerations, it is clear that there can hardly be any explanation of the ever-present residual lesions found in kernicterus other than hypoxemia on the basis of anemia.

SUMMARY AND CONCLUSIONS

Two representative cases are presented of patients with kernicterus who survived the acute stage but manifested persistent neurologic sequelae and died later of an intercurrent disease.§ Microscopic study of the brains revealed pathologic alterations corresponding to those produced by hypoxemia of varying etiology. Pathogenic analysis of the changes and the "topistic" pattern showed such a distinct relation that it is justifiably concluded that the cerebral pathologic changes in those surviving cases of kernic-

§ The attending physician of both patients was Prof. W. Catel, of the pediatrics clinic of the University of Leipzig. He referred the brain in both cases to this institution.

terus with residual neurologic symptoms are due to hypoxemia from hemolytic anemia. There was a definite correlation between the extrapyramidal symptoms manifested by the patients and the selective alterations in the brain. Many investigators have attempted to correlate the cerebral lesions with jaundice, but we believe that the jaundice per se is of no pathogenic importance in the production of the cerebral lesions in kernicterus.

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Benign Postinfectious Disorder of Anterior Midbrain

Alternating Contraction Anisocoria, Combined with General Fatigue and Peripheral Neuritis

OTTO LOWENSTEIN, M.D., New York

During periods of increased incidence of endemic virus infections, I have observed a number of patients who, after the acute stage of infection had passed and the temperature had returned to normal, complained of prostration with general fatigue and increased fatigability, mental depression, and symptoms of peripheral mononeuritis or polyneuritis. Among them, a group of 22 cases was found to show a pupillary syndrome of alternating contraction anisocoria. This syndrome indicates involvement of the anterior midbrain and characterizes the condition as virus encephalomyelitis.[1]

The patients were neurologically examined an average of six weeks after the onset of the disease. The infection itself was usually described as having started with a sudden rise in temperature. The temperature did not rise to more than 102 F in any of our cases, and in seven cases the rise was not expressly reported but on analysis of the history appeared to have occurred. In no case was disturbance of consciousness encountered during the acute stage, but some patients were reported to have shown a marked degree of motor restlessness, headaches, sensations of pain and heaviness in the limbs, and hypersensitivity of the skin and muscles. The condition of prostration was present in all cases, including those in which an acute rise of temperature had not been observed.

When the patients came for neurological examination, they invariably complained of constant painful fatigue which either was present upon awakening in the morning or appeared almost immediately after slight effort. In addition, they complained of motor weakness in one or several limbs and, frequently, pain or paresthesias in the distal parts of the lower or upper extremities.

The neurological examination did not reveal any pathology except for peripheral mononeuritis or polyneuritis, which was pronounced in some cases but in other cases appeared in the mild form of hypersensitivity of the nerve stems to slight pressure. Laboratory studies included blood counts, urinalysis, Kline test, and determinations of nonprotein nitrogen, blood sugar, serum cholesterol, and sedimentation rate, all of which gave normal values. Spinal fluid studies included cell counts; pressure readings; total protein, sugar, chloride, and colloidal gold curve determinations, and Wassermann test, all being normal. Papillostasis, anomalies of eye muscle movements, or absence of pupillary reflexes was never detected. Varying degrees of unilateral or bilateral alternating contraction anisocoria were found in each case.

Alternating contraction anisocoria as a clinical syndrome was described in a previous paper.[1] In cases in which the syndrome is unilateral, the two pupils remain equal in

From the Department of Ophthalmology (Laboratory of Pupillography), Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

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size during light stimulation of one eye but become unequal when the other eye is stimulated. In the bilateral syndrome, anisocoria results from light stimulation of either eye, but, regardless of the side stimulated, the homolateral pupil always becomes smaller than the consensually reacting pupil. The lesion producing alternating contraction anisocoria is located in the anterior part of the midbrain. The focus must include one or more lesions in both the first afferent pupillary neuron * (from the retina to the pretectal area) and the second afferent neuron (from the pretectal area to the third nerve nucleus) of the light reflex arc. Of 158 cases in which alternating contraction anisocoria was studied,[1] 35% were caused by specific and nonspecific infections of the central nervous system, 17% by vascular pathology, 14% by heredodegenerative conditions, and 11% by multiple sclerosis. In addition to the postinfectious neurological diseases noted above, alternating contraction anisocoria constitutes part of a syndrome characteristic of benign subchronic encephalomyelitis.

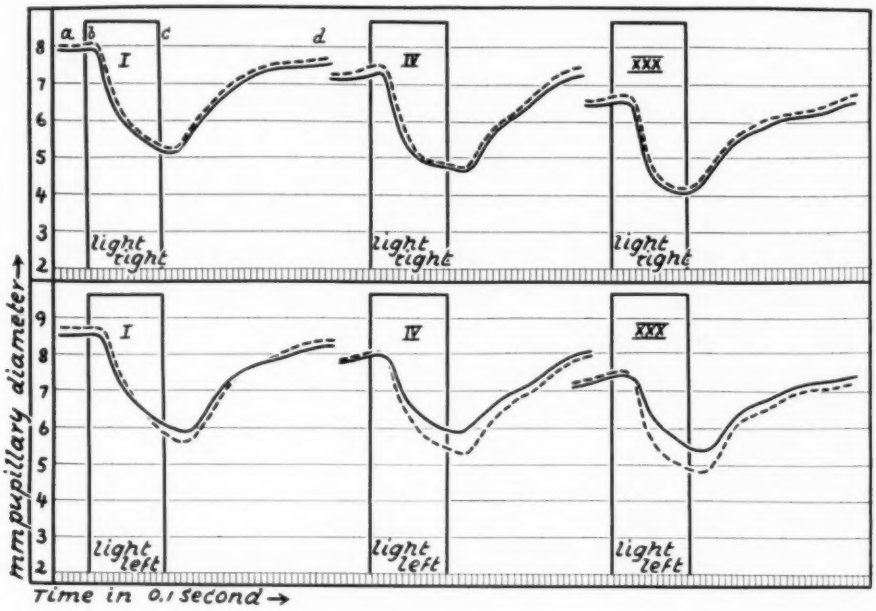


Fig. 1.—Pupillogram of Case 1, of Jan. 21, 1950.

The pupillary diameter (in millimeters) is plotted against time (in 0.1 second), whereby the solid line represents the right pupil, the broken line the left pupil.

First line: When the eyes are adapted to the dark red-infrared illumination (*a*), the pupils are equal, at 8 mm. When the right eye is exposed to a light stimulus of 15 ft-c. intensity and one-second duration, while the left eye remains in darkness (*b—c*), the two pupils contract equally; they redilate during the dark interval which follows each light stimulus (*c—d*). The 1st, 4th and 30th reactions of a continuous series of reflexes are shown.

Second line: When the left eye is similarly exposed to the stimulating light, while the right eye remains in darkness, the direct reaction of the left pupil is more extensive than the consensual response of the right pupil, so that the two pupils become unequal during the contraction phase.

DESCRIPTION OF CASES

Twenty-two cases of benign subchronic encephalomyelitis were observed in which alternating contraction anisocoria was the

* In agreement with the terminology I have used in previous studies (References 1, 2, and 3), the intraretinal neurons are disregarded and the term first neuron is applied to the retinal ganglion-cell layer, which sends its fibers through the optic nerve, chiasm, and tract.

sole sign of cerebral involvement. In all of them the symptoms subsided under nonspecific protein treatment within a period which varied from three months to three years. Three representative cases will be described.

CASE 1.—A 27-year-old pianist, mother of two healthy children aged 2 and 1 year, had a period of elevated temperature, up to 100 F, for about five days. Subsequently she complained of a constant feeling of fatigue and general weakness which made it impossible for her to do her daily housework. On playing the piano, she felt immediate fatigue and inability to move her arms and fingers normally and experienced pain in her finger tips.

Two pupillograms had been taken eight and four years before the onset of the disease, when the patient was a student in good health and served as one of the normal experimental subjects in this laboratory. At those times her pupils were large and equal and reacted normally. She was seen as a patient for the first time on Jan. 21, 1950. The neurological examination showed motor weakness in both upper extremities, particularly below the elbows. The radial nerves were more severely involved than the ulnar and median nerves, and the right side was more impaired than the left.

The pupillogram revealed the syndrome of unilateral alternating contraction anisocoria. When the right eye was stimulated by light, both pupils reacted normally and equally. However, when the left eye was stimulated, the consensual reaction of the right pupil was less extensive than the direct reaction of the left pupil, so that, at the peak of contraction, inequality existed. This anisocoria increased on repetition of the light stimulation, to reach a maximum of 0.93 mm. (Fig. 1).

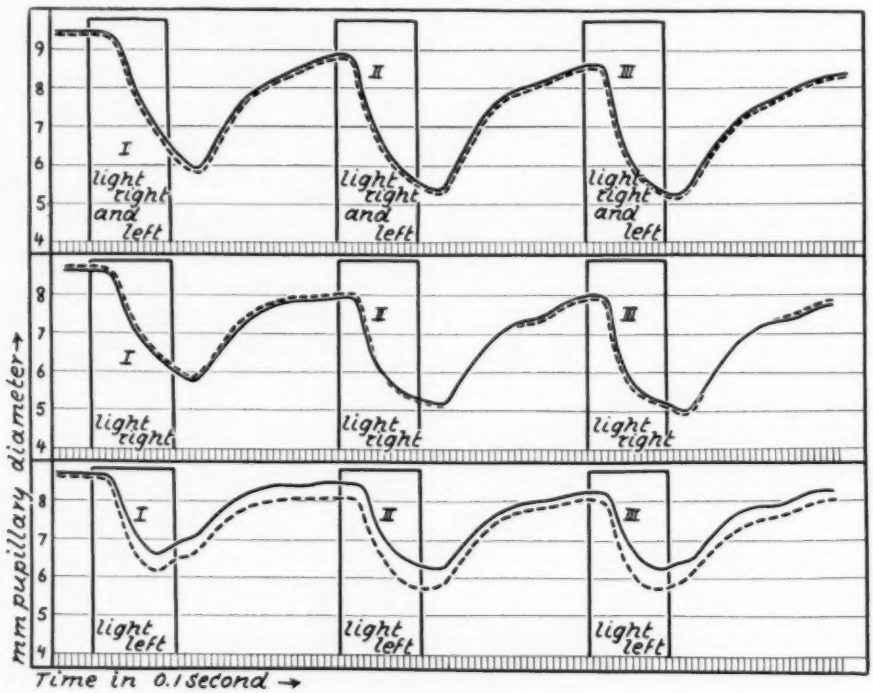


Fig. 2.—Pupillogram of Case 1, of March 6, 1950.

The first, second, and third reactions of three series of light reflexes are shown. When the two eyes are simultaneously stimulated (first line) or when the right eye alone is exposed to the light stimulus (second line), the two pupils react normally and no anisocoria appears. In contrast, the pupils react poorly and unequally when the left eye is stimulated; the direct contraction of the left pupil is more extensive than the consensual contraction (third line) of the right pupil.

By March 6, 1950 (Fig. 2) the pupillary syndrome had become more marked, but by May 8 and July 1, 1950, definite improvement was noted (Fig. 3).

On April 20, 1951, the patient still suffered from severe generalized fatigue, which prevented completion of her normal daily duties. By the spring

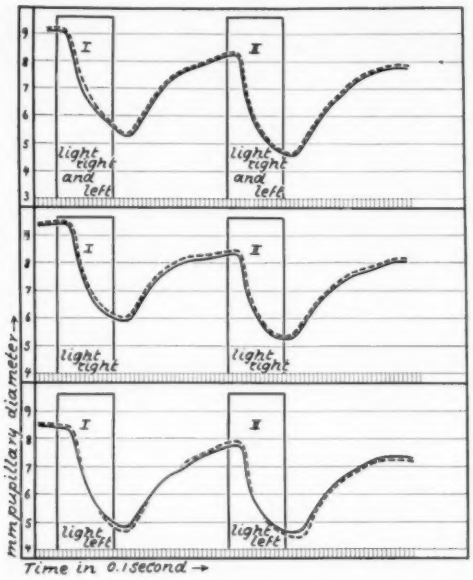


Fig. 3.—Pupillogram of Case 1, of May 8, 1950. The first two light reactions of each series are shown. As compared with the findings of March, 1950 (Fig. 2), the pupillary reactions are greatly improved. The sole remaining pathological sign appears in the third line: When the left eye is stimulated while the right eye remains in darkness, the consensual response of the right pupil is less extensive than the direct reaction of the left pupil.

of 1953 she had recovered completely. Pupillograms taken since then have been entirely normal (Fig. 4).

This case was one of acute virus infection contracted at a period when such conditions were prevalent. After the acute stage had terminated, a syndrome of general fatigue with slight reactive mental depression, polyneuritis in both upper extremities, and unilateral alternating contraction anisocoria was present. The pupillary syndrome was the only sign of involvement of the central nervous system. Within a period of from two to three years all symptoms gradually disappeared and the patient recovered completely.

CASE 2.—The patient was a 37-year-old unmarried woman, whose previous history was noncontributory. In January, 1953, she suffered from an acute virus pneumonia. Her temperature returned to normal after treatment with oxytetracycline (Terramycin). One week later her lower extremities became weak and anesthetic. She was taken to a hospital, where she complained of paresthesias, particularly pins-and-needles sensations, and muscle twitchings in both lower extremities. A diagnosis of "virus pneumonia, followed by peripheral polyneuritis" was established. After about a week she was dismissed from the hospital, but the symptoms of fatigue, paresthesias and weakness in all four extremities, and mental depression persisted.

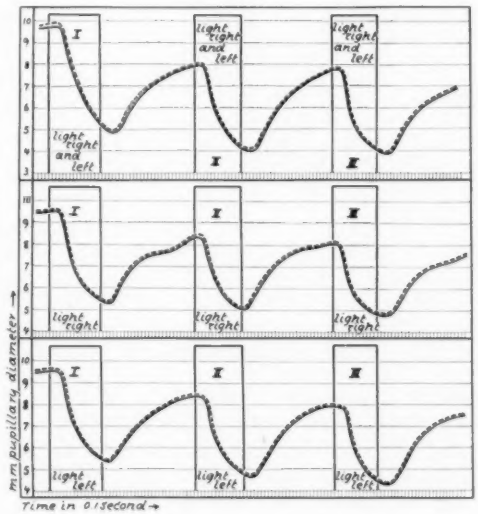
When I first saw her, on March 22, 1953, the general neurological examination showed asymmetric ankle reflexes. The motor functions were unimpaired. Touch and pain sensations in the lower extremities were stated to be more intensive than a few weeks previously, but they were still below normal. Mentally, she was depressed, hyperexcitable, and complaining of extreme generalized fatigue.

Pupillographic studies showed unilateral alternating contraction anisocoria, complicated by a slight impairment of the right sympathetic dilator pathway:

1. In the dark-adapted state, the left pupil was 0.9 mm. larger than the right one.

2. When the left eye was stimulated by light, the existing static anisocoria diminished, and almost disappeared during the second light reflex. In contrast, when the right eye was stimulated, the anisocoria remained. Similar behavior was found upon illumination of longer duration: When the left eye was illuminated for three minutes, the pupils became nearly equal, but they remained un-

Fig. 4.—Pupillogram of Case 1, of Feb. 4, 1954. The first three reactions of each series of light reflexes are shown. All pathological signs have disappeared. The pupils react normally and equally when both eyes (first line) or when either eye alone (second and third line) is exposed to the light stimuli.



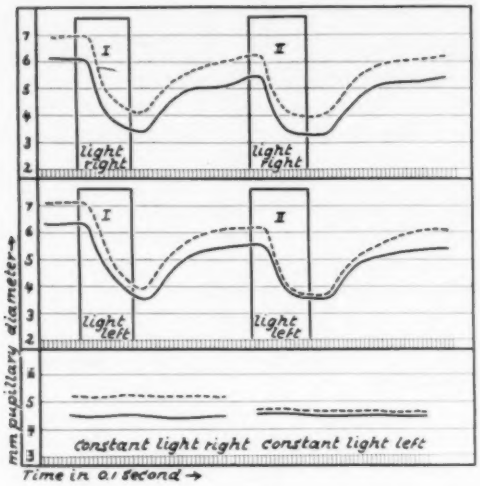


Fig. 5.—Pupillogram of Case 2, of March 17, 1954.

This case differs from Case 1, in that the pupils are unequal in darkness, owing to a partial lesion of the right peripheral sympathetic path.

First line: When the right eye is stimulated by light, the two pupils react equally, and the existing anisocoria remains unchanged.

Second line: When the left eye is stimulated, the consensually reacting right pupil contracts less than the directly reacting left pupil; consequently, the pupils become equal at the peak of contraction.

Third line: The pupils remain unequal when the right eye is exposed to the stimulating light for three minutes, but anisocoria disappears when the left eye is similarly illuminated.

equal when the right eye was illuminated. Therefore, the direct reaction of the left pupil was more extensive than the consensual response of the right pupil, but the pupils reacted equally when the right eye was stimulated.

This case was one of virus infection (virus pneumonia) with participation of the central nervous system, characterized by polyneuritis, unilateral alternating contraction anisocoria, feeling of extreme general fatigue, and mental depression. The case showed a tendency toward improvement at the end of two months and was practically cured in six months.

Case 3.—The patient, a 26-year-old woman, had never previously been ill. She married at the age of 21 and gave birth to a boy, in good health, at the age of 24. In July, 1951, she suffered from a "bad cold," with temperatures up to 100 F. She did not interrupt her work, but after her temperature had returned to normal, she did not recover. She suffered from extreme fatigue and felt weakness in her right leg and arm. She always felt sleepy but had difficulty in falling asleep when she went to bed.

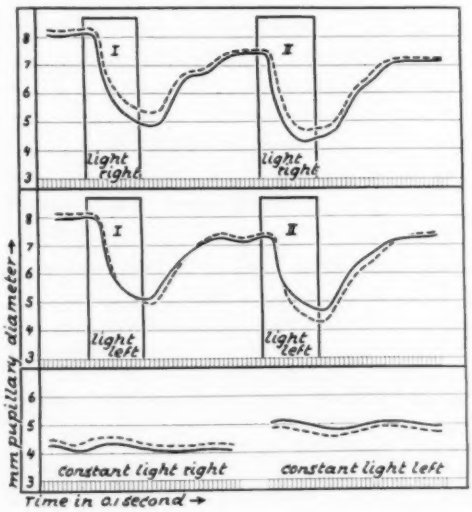
At the first examination, she complained of constant fatigue, even after a good night's sleep, and of difficulty in making decisions about the most insignificant matters. On neurological examination, she did not show any pathological signs; motor weakness was no longer present. Mentally, she was excitable, tired, and slightly depressed.

Pupillographic studies showed bilateral alternating contraction anisocoria. When the right eye was stimulated by light, the right pupil contracted more than the left pupil; when the left eye was stimulated, the left pupil contracted more than the right one.

The patient was given a period of complete rest of three months, with injections of cyanocobalamin (vitamin B_{12}) and foreign protein. Since, after eight weeks, fatigue and depression had not disappeared, she was given a series of 15 noncomatous (subshock) insulin treatments for a period of 30 days, at the end of which time she had recovered.

The case was one in which the acute stage of infection had passed almost unnoticed, but in which the patient subsequently showed a mild peripheral neuritis of the right upper and lower extremities, bilateral alternating

Fig. 6.—Pupillogram of Case 3, of Oct. 5, 1951. The directly reacting pupil always contracts more extensively, and therefore becomes smaller, than its consensually responding fellow pupil. This is found both in response to short light stimuli (first and second lines) and during illumination of longer duration (three minutes, third line).



contraction anisocoria, general fatigue, and mental depression. The condition subsided within three months.

CLINICAL CONSIDERATIONS

The clinical courses of the remaining 19 cases were essentially similar to that in the 3 cases outlined above. They differed only as to the degree of severity of the symptoms, the extent of peripheral sensory or motor involvement, and the duration of the illness. The alternating contraction anisocoria was either unilateral or bilateral, with the resulting anisocoria varying from 0.3 to 1.5 mm.

From the clinical standpoint, there cannot be much doubt that these cases resulted from virus encephalitis, since all occurred during periods of increased incidence of endemic virus infections. The exact nature of the underlying process could not be determined, as the patients all recovered and histological studies could not be made. Clinically, the cases differed from Economo's encephalitis epidemica, as to both symptoms and course. None of the symptoms characteristic of Economo's epidemic encephalitis were present, such as changes in personality, hyperkinesias, rigor of muscles, and Parkinsonism, and, in contrast to Economo's encephalitis, tendencies toward improvement could be observed early in the course of the disease. Further, radiculitis and peripheral mononeuritis or polyneuritis are rare in Economo's disease, although they have been described.[4]

In the differential diagnosis, the exclusion of initial multiple sclerosis may sometimes be difficult. However, multiple sclerosis rarely follows an acute febrile disease; it is only rarely associated with pain, and its course differs by occurring in attacks, showing rapid remissions rather than slow, even recovery.

Syphilitic conditions may be excluded by the patient's history and by the results of blood and cerebrospinal fluid tests.

The association of encephalitis with peripheral neuritis has frequently been described in the literature. Wernicke's so-called polioencephalitis acuta haemorrhagica superior, in which the clinical picture of encephalitis is found associated with clinical pictures of polyneuritis, is not true encephalitis, either pathologically or etiologically. However, many cases have been described in which endemically occurring encephalitis was associated with polyneuritis.† In this respect, the present communication does not report anything new. However, it presents the possibility of establishing the correct diagnosis in cases in which no clinical signs of encephalitis are observed, but in which symptoms of peripheral neuritis can be shown to be combined with a symptom of the anterior dorsal midbrain, i. e., alternating contraction anisocoria.

The alternating contraction anisocoria is due to a lesion in the anterior midbrain, probably of the white matter. The subjective symptoms, such as general fatigue, sleepiness combined with insomnia, and increased fatigability and excitability, are manifestations of pathological processes in the central nervous system. The mental depression is probably a reaction of the personality to the feelings of insufficiency caused by extreme fatigue. The entire condition gradually subsides.

One should not, of course, be tempted to consider each encephalitis as benign solely because it may be connected with alternating contraction anisocoria. This syndrome, which can be considered primarily as a means of localizing a lesion, may occur in all types of encephalitis, particularly in Economo's disease, syphilitic encephalitis, syphilitic meningitis, and, in addition, multiple sclerosis. However, these diseases are not essentially connected with mononeuritis or polyneuritis. It is the combination of alternating contraction anisocoria with peripheral neuritis, general fatigue, increased fatigability, and mental depression which, following in the wake of acute virus infection, constitutes, in our cases, a syndrome of benign nature.

† Reference 4, p. 586.

SUMMARY

A syndrome is described which occurs as a sequela of virus infections and consists of excessive general fatigue, increased fatigability, mental depression, mononeuritis or polyneuritis of differing extent and intensity, and the pupillary sign called alternating contraction anisocoria.

The course of the acute infection may be mild, and may even pass unnoticed. The symptoms of neuritis may be severe or mild, and may even be limited to increased sensitivity of the nerve stems to pressure; the mental depression may be mild, or even absent. The presence of alternating contraction anisocoria reveals, in the absence of other neurological signs, involvement of the central nervous system. It permits differentiation of this involvement from functional disorders and determination of its organic nature. The differential diagnosis of this syndrome versus that of Economo's encephalitis epidemica, syphilitic conditions of the central nervous system, and multiple sclerosis is discussed.

All 22 cases observed were cured without sequelae in a period of three months to three years; the syndrome is therefore considered to be benign. A period of complete physical rest, parenteral administration of foreign proteins, and, in some cases in which the mental depression was pronounced, noncomatous insulin subshock treatments appeared to be of beneficial effect.

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Blood Chemistry Studies in Bilateral Ligation of Anterior Cerebral Arteries

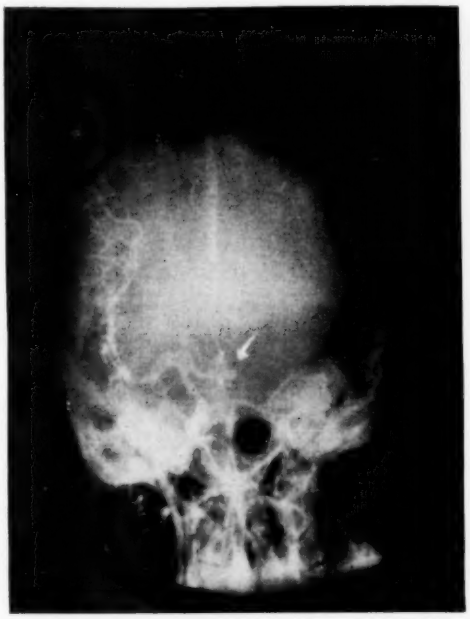
E. S. GURDJIAN, M.D.
and
J. E. WEBSTER, M.D., Detroit

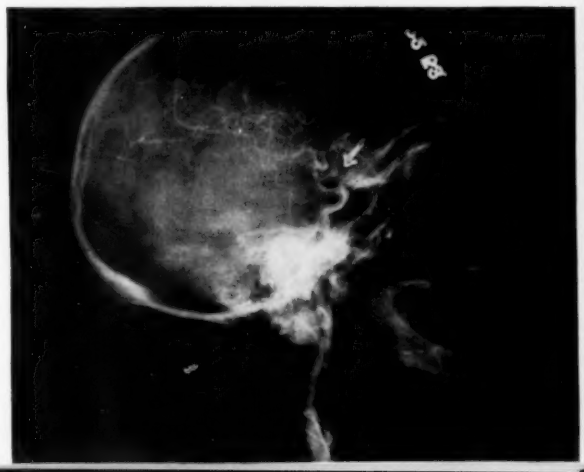
In two patients with aneurysms of the anterior communicating artery it was necessary to ligate the anterior cerebral arteries proximal and distal to the sac. Both patients were conscious and alert immediately following recovery from anesthesia. It has been reported that ligation of both anterior cerebral arteries near or at their origin from the internal carotid arteries results in a fatality with or without immediate postoperative unconsciousness. This paper reviews these experiences toward accumulating more data pertaining to the surgical treatment of aneurysms of the anterior communicating artery.

REPORT OF CASES

CASE 1.—M. M., a 40-year-old Negro woman, was admitted in a semiconscious state. There was a history of an automobile accident five years earlier with no serious head injury. However, subsequently she complained of right-sided headaches intermittently. Ten days before admission the headaches became severer and were associated with vomiting. Five days before admission there was numbness of the left arm and leg, with weakness of both. The patient was a thin woman, with bilateral papilledema. There was left hemiparesis associated with left hemihypalgesia. A left Babinski sign was present. Deep tendon reflexes were increased on the left side. Serial angiograms revealed an aneurysm of the anterior communicating artery about 7 mm. in size (Figs. 1 and 2). A ventriculogram showed slightly dilated ventricular system. A left-sided angiogram was found to be normal. In view of the presence of a small bony defect in the left side of the skull in the frontal region, a biopsy was done, which showed the bone to be involved by a hemangioma.

Through a bifrontal bone flap the aneurysm of the anterior communicating artery was exposed between the hemispheres. It was necessary in the course of removal of the aneurysm to ligate both





Figs. 1 and 2.—Aneurysm of the anterior communicating artery filled from the right side.

From Wayne University Neurosurgical Service, Grace Hospital.

Aided by the Kresge Fund.

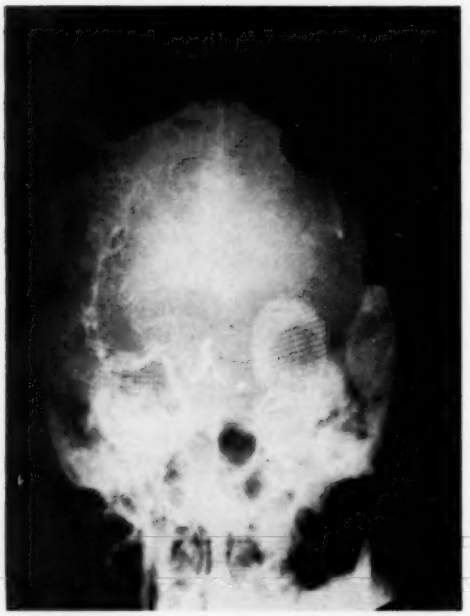


Fig. 3.—Postoperative angiogram showing complete absence of the anterior cerebral artery.

anterior cerebral arteries proximal and distal to the sac. The aneurysmal sac was removed in toto (Figs. 3 and 4).

The patient was conscious after recovery from anesthesia. She remained alert for about 36 hours and then became drowsy. Three days later she was able to move all extremities but she was unresponsive. The blood pressure, respiration, and pulse were normal. Spinal puncture revealed a normal pressure with xanthochromic fluid. Five days after operation the patient would talk freely but was

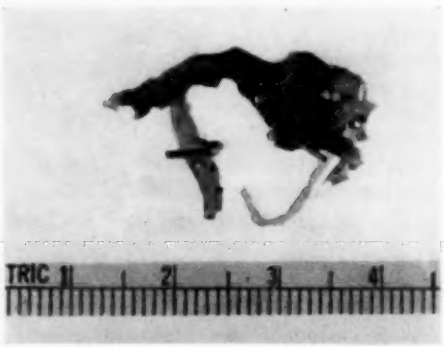


Fig. 4.—The excised aneurysmal specimen.

TABLE 1.—*Blood Chemistry Studies (Case 1)*

	Sodium				Potassium				Chloride Plasma			
Date	Normal Value, Mg/ 100 Cc.	Found Value, Mg/ 100 Cc.	Normal Value, mEq/L	Found Value, mEq/L	Normal Value, Mg/ 100 Cc.	Found Value, Mg/ 100 Cc.	Normal Value, mEq/L	Found Value, mEq/L	Normal Value, Mg/ 100 Cc.	Found Value, Mg/ 100 Cc.	Normal Value, mEq/L	Found Value, mEq/L
7/21	300-330	388	130-144	173	16-22	15.8	4.1-5.6	4.1	570-620	721	97-107	121
7/31	300-330	405	130-144	176	16-22	24.2	4.1-5.6	6.2	.....	...	.....	...
8/8	300-330	366	130-144	159	16-22	15	4.1-5.6	3.8	570-620	693	97-107	118
8/11	300-330	399	130-144	173	16-22	25	4.1-5.6	6.4	570-620	723	97-107	124
8/13	300-330	362	130-144	157	16-22	22.4	4.1-5.6	5.7	570-620	599	97-107	102
8/20	300-330	356	130-144	155	16-22	21	4.1-5.6	5.5	570-620	622	97-107	107
8/21	300-330	335	130-144	146	16-22	21	4.1-5.6	5.5	570-620	637	97-107	109
8/24	300-330	356	130-144	155	16-22	23.4	4.1-5.6	6.0	570-620	640	97-107	109
9/11	300-330	348	130-144	151	16-22	20	4.1-5.6	5.1	.....	...	.....	...

TABLE 2.— *Blood Chemistry Studies (Case 2)*

	Date	Normal Vol/ 100 Ml.	Found	Normal mEq/L	Found
CO_2-combining power	7/11	53-75	66	24-35	30
Chloride, plasma					
As NaCl	7/11	570-620	592	.....	..
As Cl	....	.....	..	100-106	101
Sodium, serum	7/11	.....	..	136-145	145
Potassium, serum	7/11	.....	..	3.5-5.0	4.5

		Normal	Found
Glucose	6/12	60-90 mg/100 ml	99
Urea N	6/12	10-15 mg/100 ml	7
Serum amylase	6/14	80-180 units/100 ml	68

somewhat confused. Blood chemistry studies revealed a severe degree of hypernatremia, hyperchloremia, and hyperkalemia (Table 1). At first, forcing fluid by tubes and vein did not help. Later, with forced fluids and the use of mercurial diuretics, the patient made a complete recovery from the imbalance of the blood chemistry. About two months after entrance into the hospital she was discharged (Figs. 5 and 6). In many ways she had the mental processes of a lobotomized person. When she was seen nine months after operation her mental processes were much more normal. She did a great deal

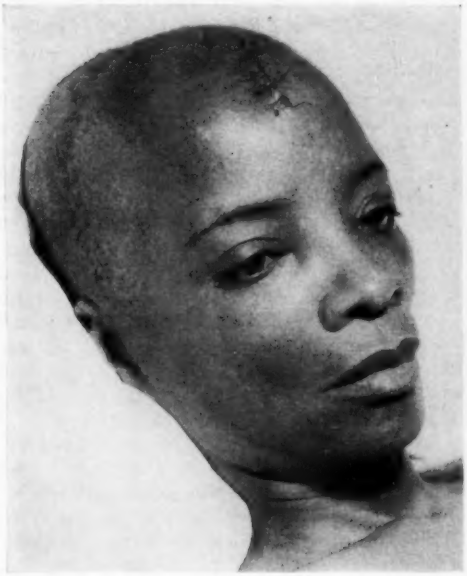
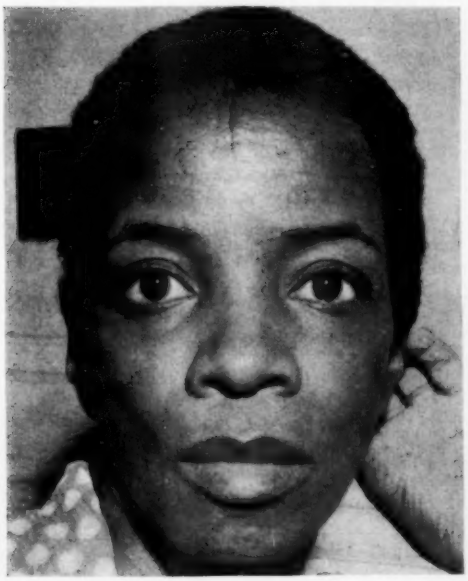
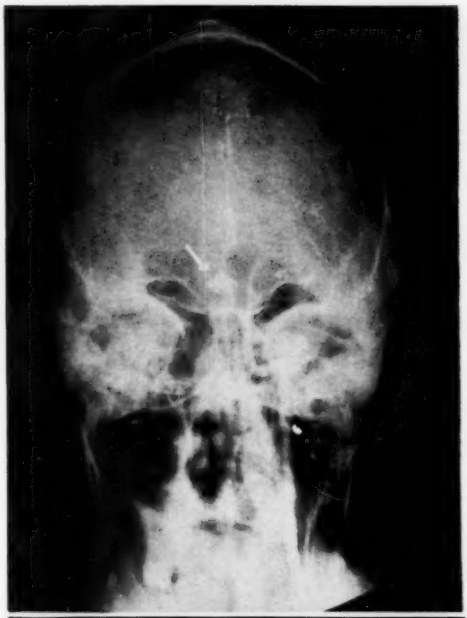


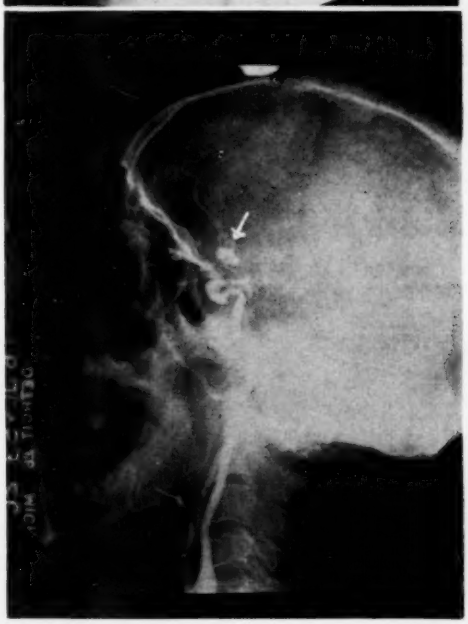
Fig. 5.—Appearance during the hyperosmolarity of the blood.

Fig. 6.—Appearance after recovery.



Figs. 7 and 8.—Aneurysm of the anterior communicating artery filled from the left side.





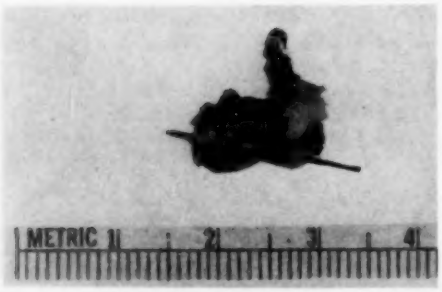


Fig. 9.—Excised specimen.

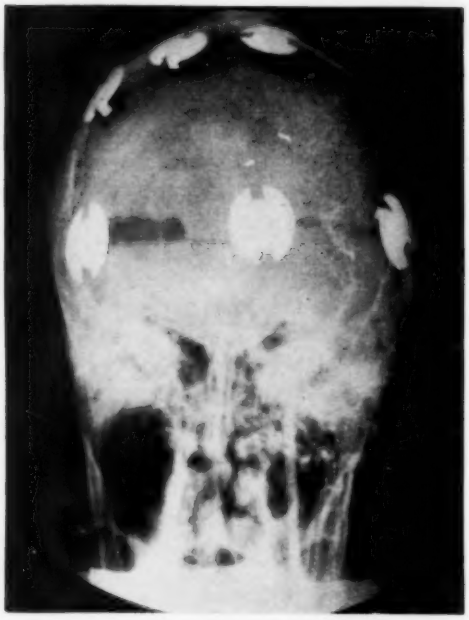
of the housework at home, was cooperative, and carried on activities spontaneously. Her daughter felt that her condition was just about as good as her preoperative state. When seen 18 months after surgery, the patient was normal in behavior. There has been one attack suggesting an epileptic equivalent. Her blood chemistry was checked on two occasions during the follow-up period. The findings were normal.

Case 2.—A. N., a 53-year-old white man, four days prior to admission developed a state of disorientation and lack of coherence. Seven years previously the patient had sustained a skull fracture in a fight. There was a history of alcoholism and pancreatitis. Examination revealed a confused, noncommunicative, apathetic patient with a right-sided facial weakness associated with right hemiparesis and complete motor and partial sensory aphasia. The blood pressure was 120/78. The left carotid angiogram showed an aneurysm involving the anterior communicating artery (Figs. 7 and 8). The right carotid angiogram was normal. The cerebrospinal fluid was xanthochromic.

Through a bifrontal craniotomy the aneurysm was exposed between the two hemispheres at the site of the anterior communicating artery. It was found necessary to do a four-limb clipping of the aneurysm, and the sac was removed in toto (Figs. 9, 10, and 11).

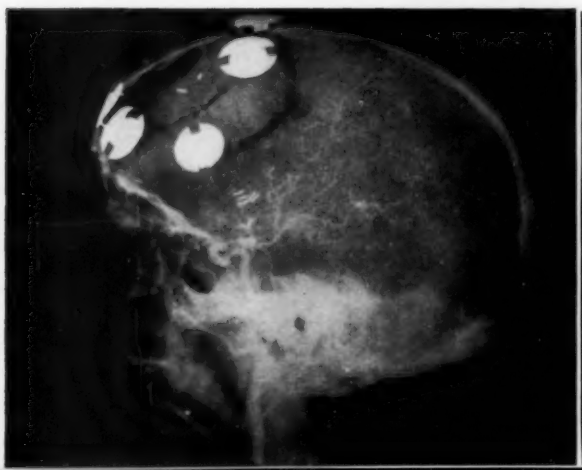
Immediately after recovery from anesthesia the patient was as bright and alert as prior to the operation. He still had the right-sided weakness and the motor and partial sensory aphasia. Two weeks after the operation the patient suddenly stopped breathing and in a matter of minutes was dead. Blood chemistry studies showed no unusual chemical derangement, the last group of examinations having been done the day before the patient's death (Fig. 12).

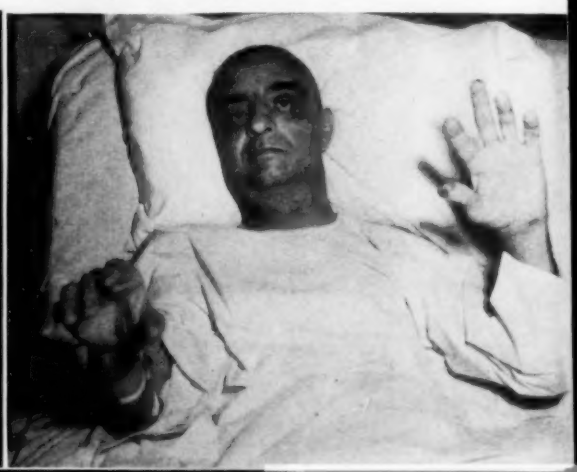
Autopsy showed normal-appearing frontal lobes. There was an area of infarction in the distribution of the middle cerebral artery on the left side, clinical symptoms from which caused the patient to be hospitalized. There was necrosis of the anterior portion of the corpus striatum bilaterally (Fig. 13). No other abnormalities were noted in the body suggesting other than a cerebral cause for the sudden death.



Figs. 10 and 11.—Postoperative angiograms showing absence of the anterior cerebral artery distribution.

Fig. 12.—Postoperative photograph showing right upper limb weakness. This patient had no hyperosmolarity of the blood.





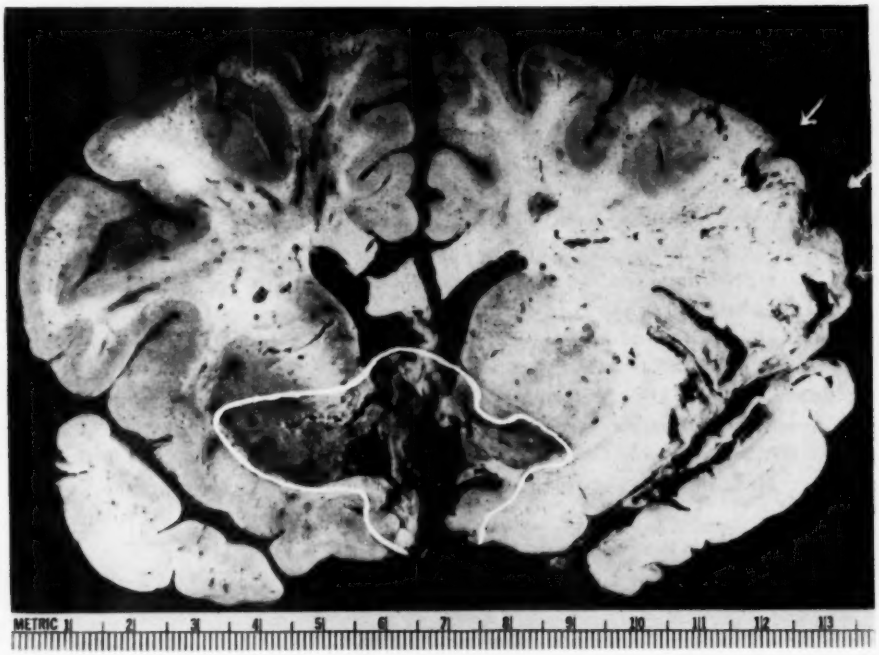


Fig. 13.—Specimen of brain showing area of softening in the distribution of the recurrent branch of the anterior cerebral artery on both sides. Also note area of infarction in the left middle cerebral artery distribution.

COMMENT

Dandy,[9] in 1946, correlated the effects of ligation of the anterior cerebral artery with unconsciousness. He concluded that a cause for unconsciousness was an ischemia with necrosis of the anterior third of the corpus striatum. He also noted that in the patient with ligation of the anterior cerebral arteries at the internal carotid, both frontal lobes looked surprisingly normal and were not soft or necrotic. The striatal softening was thought to be due to occlusion of the medial striate arteries, or Heubner's arteries. Poppen [17] stated that where the anterior cerebral arteries were ligated superior to the anterior communicating there were no effects. In seven cases the left anterior cerebral artery was ligated without disturbance in consciousness. Poppen concluded that a left anterior cerebral artery could be safely ligated above the anterior communicating if the blood pressure was within an elevated level. Ligation of one anterior cerebral artery at its origin from the internal carotid has been done by many authors, but in case of a thrombosis with eventual involvement of Heubner's artery serious results may obtain.

Duret,[11] in 1873, portrayed the presence of striate branches from the anterior cerebral artery, but emphasized the branches from the middle cerebral to this region. The latter concept was further exaggerated by Charcot.* Heubner † correctly identified the recurrent branch of the anterior cerebral artery supplying the corpus striatum. Ayer and Aitken,[3] Beevor,[4] and Alexander [1] found that in one-fourth to one-third of cases the anterior cerebral arteries did not send branches to the corpus striatum. In such cases the corpus striatum received its blood supply from the middle cerebral and the anterior choroidal arteries. The work of Kaplan, Rabiner, and Browder [6] has further clarified the blood supply of the basal ganglia.

MacCarty and Cooper [16] reported on a patient with bilateral anterior cerebral artery

* Charcot, M., cited by Aitken.[2]

† References 12 and 13.

ligation in the course of removal of a pituitary tumor. The patient had an electrolyte derangement consisting of hypernatremia, hyperchloremia, and hypochloruria with mental depression, coma, low blood pressure, rapid respirations, and flaccidity of the body musculature. The patient died 40 days postoperatively, and necropsy showed a massive infarction in both frontal lobes and both corpora striata. No renal disease was found. Other reports also have related the retention of sodium and chlorides in several types of brain damage. These have included patients with pituitary tumors, lobotomies, and head injuries in which the inferior surfaces of the frontal lobes and/or the hypothalamus was damaged, in 16 out of 18 cases reviewed by Cooper [7] in 1953.

The mechanism for the production of this electrolyte imbalance is not clear. Lewy and Gassman [14] found elevated chlorides in blood of cats after injury to the preoptic nuclei of the hypothalamus. Elevated serum sodium has been found after injury to the ventromedian nuclei of the hypothalamus of rats for as long as three or four months, according to Stevenson, Welt, and Orloff.[19] The presence of cerebral osmoreceptor mechanisms controlling the osmolarity of the blood has been suggested by Verney.[20] The neurohypophysis may regulate the secretion of the antidiuretic hormone, which controls in part the sodium salt quantity in the blood serum. This mechanism may be aided by the production of mineralocorticoids, cortisone, and androgenic steroids secreted by the adrenal cortex through the production of corticotropin (ACTH) by the anterior pituitary.

Our living patient has shown a reversibility of the hyperosmolarity syndrome without apparently any significant therapy except for forced fluids and mercurial diuresis. The brain damage resulting from the bilateral anterior cerebral artery occlusion in this instance is not known. Judging from our other patient and the comparable patient of Dandy, the necrosis is limited to the anterior portion of the corpus striatum. The frontal lobes in both these cases showed little or no change. The blood supply to the hypothalamus may be of vital importance in the production of hyperosmolarity. It is interesting to note that our second case had no chemical abnormality in blood studies.

SUMMARY

Two patients are presented in whom an anterior communicating aneurysm was excised, necessitating ligation of the anterior cerebral arteries proximal to the aneurysm. One patient showed marked hyperosmolarity which was reversible, and she is living and well 18 months after operation. The other patient had no electrolyte imbalance, and autopsy showed necrosis and softening of the anterior portions of the corpus striatum bilaterally. The motor functions in both cases were not influenced by the bilateral ligation of the anterior cerebral arteries proximal to the anterior communicating vessel. Both patients were conscious postoperatively.

The anatomy of the circle of Willis and the branches supplying the corpus striatum and thalamus should be reevaluated. Concepts of Duret and Charcot frequently cited in modern literature do not agree with the work of Heubner, Ayer and Aitken, Beevor, Alexander, and Kaplan, Rabiner, and Browder.

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Visual and Motor Instability in Multiple Sclerosis

JENS EDMUND, M.D.
and
TORBEN FOG, M.D., Copenhagen

It is well known that patients with multiple sclerosis note fluctuations in their symptoms under certain circumstances. For instance, it is generally known among patients that they feel more uncomfortable in heat than in cold. Heat aggravates partly their general condition and partly their neurological symptoms. In addition to an exacerbation of the existing symptoms, heat may even induce new ones, such as the transient visual impairment after a hot bath. This phenomenon has also been observed during muscular exertion and after eating.

Some time ago there was in the Department of Neurology of the Copenhagen City Hospital a patient whose syndrome was dominated by such visual complaints. For this reason, we started looking for similar symptoms in other patients with the same disease. Before proceeding to general considerations regarding these visual complaints and their relation to stress, we shall briefly report this patient's history.

The patient was a student, aged 25, who from 1949 had noted visual impairment, especially upon exertion. At the outset he experienced difficulty in reading, but gradually he also noticed visual impairment following physical exertion, such as short walks or ascending stairs. Vision began to decrease shortly after the exercise started but returned after a short rest. He also noticed that his legs tired abnormally, so that after short walks they could hardly carry him. At this stage, ophthalmologic examination showed a drop in visual acuity from 6/6 to 6/18 after running stairs. This impairment could, however, be corrected to 6/6 by +1.25 D. sph. After half an hour's rest the myopia disappeared and the patient had regained his normal vision. The visual impairment was accompanied by severe adynamia of the lower limbs, which also subsided after a rest. On his admission to the Copenhagen City Hospital, Department of Neurology, in 1952, these symptoms had perceptibly increased. The patient had become myopic also at rest and could not do without glasses, —1.50 D. sph. On admission, a diagnosis of incipient multiple sclerosis was made.

This case gave rise to the question whether similar visual fluctuations had been observed in other patients with multiple sclerosis. A study of the case records of 152 patients who had been admitted to the Department revealed that 44, or more than 25%, had had similar intermittent visual complaints, consisting in transient impairment of the visual acuity. Ten, or almost one-quarter, reported that these visual complaints occurred in connection with heat or physical exertion. In one case they followed upon meals. Only four had histories of visual field changes. On the basis of this material, it seems justified to answer the question in the affirmative, even quite decidedly, as the values must be taken to represent a minimum, because the data were not directly asked for but were supplied more or less spontaneously.

In the case of the student, and in another 10 patients, the visual impairment followed upon exercise or exposure to heat. In our endeavor to arrive at a method for reproducing these visual phenomena, we found heating in a hot-air bath for 25 minutes to be the easiest and most effective procedure.

MATERIAL AND METHOD

Forty-five patients with multiple sclerosis were subjected to the heating procedure. To this end,

From Copenhagen City Hospital, Department of Neurology; Chief, Knud Krabbe, M.D.

TABLE 1.—*Sex Ratio and Age Distribution of Multiple Sclerosis Patients*

Age, Yr.	No. of Cases	Sex
15-19	1	1 male
20-29	12	7 females 5 males
30-39	17	10 females 7 males
40-49	10	5 females 5 males
50-59	5	4 females 1 male
Total	45	26 females 19 males

we used a box with incandescent lamps of the type ordinarily used in physical therapy. The box is so large that the patient can sit inside it, with only his head exposed, through an opening in the lid of the "barrel." There is, in addition, a smaller opening, which leaves room for the patient's left hand, as well as the tubes to and from an ordinary blood-pressure apparatus, so that pulse and blood pressure (palpatory) could be controlled throughout the experiment.

During heating, the temperature in the box rises to about 55 C, or to slightly over 60 C. In some of the experiments we took the body temperature. It never rose by more than a few tenths of a degree. In a few experiments we used only local heating, and in others we used a slightly different arrangement, but the principle was the same.

Various measurements were performed, and in a few cases analyses of the blood serum (for blood sugar and potassium) were made. In a few, also, determination of sweat secretion, chronaxie measurements, and electromyography were done.

As a rule, the heating period was about 20 minutes.

In 29 cases, the vision was determined before, during, and after the experiment. We shall report only the visual acuities determined by an ophthalmologist. Most of the patients were clinically "tested" before and after the experiments. This "testing" was restricted to the items we desired to study; e. g., measurement of chronaxie had to be done immediately after the procedure and therefore excluded a more thorough neurological examination.

TABLE 2.—*Results of Heating in Forty-One Patients Classified According to Severity of Disease*

	Total No.	Positive	Negative	Slightly Positive
Severe sclerosis	3	3	0	0
Fairly severe	4	4	0	0
Moderately severe	14	14	0	3
Rather mild	12	9	3	4
Mild	8	2	6	0
Total	41	32	9	7

In this paper we shall report only the ophthalmological and the ordinary clinical examinations. The results must, therefore, be regarded as absolute minimum values.

By the way of control, normal subjects and patients with other neurological disorders were subjected to the same heating procedure. The control material is not, however, sufficiently large to justify an evaluation of the specificity of the test in multiple sclerosis.

Table 1 shows an ordinary age distribution in a series of patients with multiple sclerosis. The male preponderance is due to chance—a result of the small numbers involved.

RESULTS

Ordinary Clinical Examinations.—This group includes only 41 patients, as 2 were examined only with a view to sweat secretion, 2 with a view only to vision, and for 1 the data have been lost.

Table 2 gives the result of heating in 41 cases classified according to the severity of the disease. "Severe" sclerosis means that the patient was bedridden, the disease showing marked and diffuse spread. All three in this category gave highly positive reactions. "Fairly severe" means that the patient was unable to get about. All four patients showed highly positive reactions. "Moderately severe" means that the patient could walk and stand. The gait was poor and with a stick, but the patient was able to get about. All 14 reacted positively, but 3 of them gave only slightly positive responses. "Rather mild" is a state in which the patient was able to get about but exhibited several symptoms. Nine out of 12 gave positive reactions, but it was only slight in 4. Three had negative reactions. "Mild" cases are those in which the diagnosis must be considered beyond doubt, but there were only a few objective signs at the time of the test. Two out of eight patients gave positive reactions.

In other words, 32 out of 41 patients showed positive reactions to heating, which was highly positive in 25. A highly positive reaction is taken to mean a considerable aggravation of the existing signs, i. e., accentuation of paresis to paralysis, or the appearance of new signs that had not been

manifest previously or that had manifested themselves during previous attacks, disappearing during the remissions. The patients who were able to walk, or just stand, after the heating are classified as slightly positive.

It is evident from Table 2 that all patients with severe and fairly severe sclerosis showed positive reactions to this stress. All nine negative cases belonged to the groups of rather mild and mild multiple sclerosis. There is a predominance of negative reactions only in the group of mild multiple sclerosis.

TABLE 3.—*Reaction to Heat in Multiple Sclerosis Patients According to Disease Activity*

	No.	Positive	Negative
Definitely active sclerosis	4	4	0
Possibly active sclerosis	6	5	1
Remissive phase	11	6	5
Stationary phase	12	9	3
Uncertain phase	8	8	0
Total	41	32 (7 slightly positive)	9

TABLE 4.—*Classification of Forty-One Multiple Sclerosis Patients According to Clinical Type*

	No.	Positive	Negative
Intermittent type	20	15	5
Progressive type	6	5	1
Grouping uncertain	15	12	3
Total	41	32	9

With regard to the reaction in relation to the disease activity, Table 3 shows that, with one exception, the patients in the groups with definitely and possibly active multiple sclerosis showed positive reactions. In the remissive phase the number of positive and negative cases is equal. In the so-called stationary phase positive responses predominate. As is well known, it is very often impossible to decide by clinical means whether the disease is active, as many plaques presumably remain completely silent. This is reflected in the last two columns of the Table, which show only 3 negative reactions among a total of 20 patients of the categories that are most uncertain with regard to activity. Of course, the numbers involved are too small to indicate whether the reaction is invariably positive in the presence of disease activity.

In Table 4 the material is classified according to clinical types. As usual, the intermittent type makes up the largest group. Although the figures are perhaps not comparable, they show a relatively larger number of negative cases in the first and last groups than in the middle, or progressive, group, which has the poorest prognosis.

A study of the reaction in relation to the duration of the disease failed to yield any data of interest. Nor could this be expected considering the marked individual variations in the intensity of this disease.

A survey of the individual clinical symptoms affected by the heating procedure must, for the reasons stated, represent absolute minimum values. Nevertheless, the results will now be given, as they include several findings of no little interest.

1. *Nystagmus.*—This includes both end-position and spontaneous nystagmus. In 10 cases a distinct exacerbation occurred during heating, beginning in the course of 10 minutes. In three instances there was no increase in this sign.

2. *Ataxia.*—It is difficult to evaluate this sign with certainty, owing to the severe pareses that were induced by the experiment. In seven cases existing ataxia was induced or increased, whereas three showed no change.

3. *Facial Palsy.*—One patient was unable to blow up his cheeks after the procedure, although before it he had shown an apparently normal function of the facial nerves. In another patient, who had already displayed some weakness in blowing up his cheeks, this sign was accentuated to palsy.

4. *Bulbar Signs.*—A bulbar, thick voice, increasing almost to bulbar palsy, was noted in one case, but several of the severe cases showed disturbances of speech of the bulbar type.

5. *Ocular Muscle Palsies.*—These were produced in five patients who did not pre-

viously have such palsies. These palsies may be specified as follows:

	No. of Cases
Bilateral ptosis	1
Bilateral ptosis plus palsy of other ocular muscles	1
Bilateral palsy of rectus muscle	1
Unilateral palsy of rectus muscle	1
Incomplete unilateral palsy of rectus muscle	1
Total	5

6. *Pupils.*—One patient exhibited transitory anisocoria during the heating.

Thus, these cranial nerve palsies were induced in a total of six patients, two of whom were in the severe, one in the fairly severe, and three in the moderately severe group; in other words, these reactions were displayed by the most severely affected patients. In this connection, one must disregard nystagmus, which may also be induced in fairly mild cases, e. g., with a recent history of a "brain stem attack."

7. *Pareses of the Extremities.*—These occurred as follows:

	No. of Cases
Bilateral pareses induced	4
Existing bilateral pareses aggravated	10
Unilateral pareses induced	5
Existing unilateral pareses aggravated	5
Total	24

Adynamia of a more than normal extent was observed in four cases. Of course, it is quite a normal thing to be weakened by great heat, but in these four cases the degree of weakness was estimated as morbid. This observation was confirmed by the patient's gait, which was compromised to an extent definitely beyond the range of normal. In three patients mild existing pareses were unchanged after the procedure; in two, severe existing pareses were unchanged, and, lastly, two patients showed a normal condition of the legs both before and after the procedure. One of the last-mentioned patients, whose paresis was characterized as severe as judged by the capacity to elevate the legs and to control the movements of the knees and feet, considerably exaggerated her symptoms. The other patient who—to our great surprise—failed to react was 57 years of age. Her symptoms were of 14 years' duration, so that the diagnosis must be considered as fairly certain. All three patients with mild pareses belonged to the group of "moderately advanced" sclerosis. One, tested in a stationary phase, gave a negative reaction to heating. The second was tested during a remission following a brain stem attack. The procedure induced a "recurrence," eliciting spontaneous nystagmus and accentuating existing ataxia, as well as a bilateral Babinski sign, which had not been present before the heating. The third patient was tested in a "possibly active phase." He had had coordinative symptoms for the past 18 months and a bilateral Babinski sign. No alteration was caused by the heating.

8. *Reflexes.*—Most of the patients in whom heating induced paralysis exhibited, if anything, weakening of the tendon reflexes, but there was no opportunity to study the reflexes systematically. However, we studied the plantar reflexes, which are not likely to be misinterpreted by an experienced neurologist.

In the following seven cases morbid plantar reflexes were produced.

Case No.	
12	Unilateral Babinski; became bilateral
14	No Babinski; alteration to unilateral Babinski
16	Absence of plantar reflexes; alteration to bilateral Babinski
18	Unilateral Babinski; alteration to bilateral Babinski
19	Unilateral Babinski plus unilateral spreading reflex, alteration to bilateral Babinski
37	No Babinski; activation to bilateral Babinski
45	Absence of plantar reflex; alteration to Babinski, which became easily exhausted. The abnormal signs were normolized 15 to 30 minutes after the procedure.

9. *Sensory Disturbances.*—Only a few patients were analyzed for sensory changes; only individual cases will therefore be reported. In one case the postural sense was lost in an area where in a previous attack it had been absent. After this attack the patient had recovered his postural sense, but

it was again lost during heating, to return slowly in the course of the next 20 minutes. In another case "uncertain postural sense" was altered to "absence of the postural sense"; this sense, however, returned later. One patient reported increasing pricking paresthesiae in both hands and forearms. For the past few years he had occasionally had the same kind of paresthesiae that were now disclosed as a part of the sclerotic syndrome. He also exhibited other signs upon evident provocation. Similar phenomena were observed in another two subjects.

Vision: Of the 45 patients subjected to the heating experiment, 29 had had ophthalmological examinations before the procedure; 15, or more than a half, responded by brief, transitory visual impairment, described by the patients as blurring. The visual acuity was determined by means of Snellen's chart at 6 meters' distance. The vision was considered impaired when the patient read at least a whole line less than prior to the procedure, i. e., a jump from 6/6 to 6/9 or from 6/9 to 6/12, etc., or more. In two instances the vision improved with stenopeic slit, and in three instances, with a myopic lens, whereas in the remaining cases the vision could not be improved by any means. In 8 of the 15 cases simplified perimetry could be carried out with red and white objects, but there was in no case a relative or an absolute central scotoma. All the patients were tested with stenopeic slit, which did not in any case impair the vision. The visual impairment set in from 10 to 15 minutes after the heating was started and lasted until about 15 minutes after it was discontinued. Permanent impairment did not result in any case. Six patients had previously noticed fluctuations in the visual acuity. All the patients who responded by visual disturbances also reacted with neurological signs.

COMMENT

It will be seen that no small proportion of patients with multiple sclerosis suffer from transient visual impairment, often elicited by stress or heat.* It is also evident that such brief, or rather transient, visual impairment may be induced or reproduced in these patients. Now, what is the cause? It is reasonable to assume that the phenomenon is due to an alteration in the function of the optic nerve, in the form either of a reaction activated in an existent plaque or of a reaction in tissue that is predestined to become the seat of a plaque.

In 19 out of the 152 cases of multiple sclerosis there was a history of retrobulbar neuritis, changes in the visual field, or ophthalmoscopic findings of definite pallor of the optic disc; in 4 there was a history of retrobulbar neuritis; in 10, pallor of the optic discs, and in 5, changes in the visual field. In other words, the optic nerve was affected in 12%. Of the 44 patients with intermittent visual complaints, 4, or 11%, had affection of the optic nerve, and of the 108 patients without intermittent visual complaints, 15, or 10.5%, had such involvement.

Thus, optic nerve involvement was equally common among patients with intermittent visual complaints and among patients without such complaints. There is, thus, no relationship between optic nerve lesion and intermittent visual complaints. As mentioned above, 15 of the 29 patients included in the heating experiment responded by visual impairment, whereas 14 did not. Of the 15 positive cases, 5, or one-third, had a history of optic nerve affection, whereas the remainder were normal in this respect. Of the 14 patients who failed to react, 4, or one-third, had a history of optic nerve lesion, whereas the remainder were normal. Even though the number of patients with optic nerve lesion among the tested patients is far higher than in the Guthrie series, an optic nerve lesion occurred with about the same frequency among the reactors as among the nonreactors; that is, there is no relationship between visual phenomena and optic nerve lesion. Examina-

* The experiments described here quite agree with the experiments made by Guthrie[7] in 1951. We had no knowledge of Guthrie's studies when we made our experiments. Our findings agree with his except for the visual fields during heating, but our explanation is different.

tions of the visual field during heating also failed to show any changes, not even a relative scotoma, which would be expected if the visual impairment bore any relation to the optic nerve lesion. Examination with stenopeic slit was performed in order to try whether a covering of the peripheral visual field, as obtained by inserting an artificial pupil, would affect the vision. If the visual impairment were due to a central scotoma, vision would be expected to be further impaired, whereas it would be improved if caused by refractive disturbances. As already mentioned, the stenopeic slit improved the vision in two cases, and in no case did it aggravate the impairment. This finding also appears to speak for the absence of any relation between the visual impairment and the optic nerve lesion. It must be emphasized, however, that the determination of the visual field during heating is extremely difficult, as the patients experience not merely impairment of vision but also an exacerbation of the general condition—heat intoxication—which makes their statements less reliable. All considered, however, neither the histories nor the experiments afforded any evidence that the visual impairment was due to alterations in the function of the optic nerve. We therefore have to consider other possibilities.

There were no alterations in the retinal blood supply or other vascular dysfunctions, as ophthalmoscopy showed no abnormality of the retina or the retinal vessels. Histamine tolerance tests failed to elicit visual phenomena.

Bouts of visual impairment, due to transitory anomalies of refraction, are sometimes encountered in certain endocrine disorders, particularly in diabetes mellitus, in which visual disturbances occur mainly in connection with sudden alterations of the condition, e. g., when insulin therapy is started or the dosage altered. These refractive changes have been related to alterations in blood sugar, increased levels entailing myopia, whereas, conversely, hypoglycemia results in hypermetropia. Such intermittent visual complaints have also been reported in other endocrine disorders, such as those of the thyroid and parathyroid glands, as well as in diseases involving alterations in the water and salt metabolism.

The mechanism of this transitory refractive change has been the object of much speculation. As shown by Elschnig,[2] these fluctuations do not occur in aphakic eyes; they must, therefore, be related in some way to the lens. Alterations in refraction are presumed to be due to a shift in the relation between the refractive indexes of the nucleus and capsule of the lens caused by capsular edema. This increases the refractive power of the eyes and renders the patient myopic. Accordingly, this form of myopia differs in essence from simple, axial myopia, which develops in the growth period, owing to elongation of the eye. The axial variety is characterized by its occurrence in early life and by being arrested when growth ceases. Lenticular myopia, on the other hand, is independent of growth and may occur at any stage of a person's life. Is there a chance that the intermittent visual disturbances in multiple sclerosis might be related to transitory refractive anomalies? In our first case, the visual impairment could to a certain extent be corrected by myopic glasses. From the age of 24 to 27, this patient had increasing myopia, and at the time of admission to the neurological department he could not do without his glasses, which were —1.50 D. sph. If this myopia, developing at the same time as the incipient multiple sclerosis, bears any relation to the disease, one would expect refractive anomalies, and particularly myopia, to be commoner in multiple sclerosis patients than in normal persons. Investigation of the refraction in the 152 patients with multiple sclerosis gave the following result:

Emmetropia	70, or 46%
Hypermetropia	41, or 27%
Myopia	41, or 27%

While emmetropia is difficult to distinguish from low-grade hypermetropia, myopia can easily be distinguished, as myopia of even 0.50 D. results in perceptible visual impairment. It is striking that 54%, or more than half of the patients, had refractive anomalies,

but it is even more surprising that 27% were myopic. The reported frequency of myopia in normal populations is extremely varied. The highest frequency has been found in the Mongolian race, particularly in Japan, where myopia has been reported in about 70%. The lowest incidence has been found in Scandinavia. In a Danish normal series of 52,000 (1927), Blegvad [1] found myopia in 5%. Similar values have been reported from other Scandinavian countries. This percentage must, therefore, be accepted as applying to the Danish population. Statistical calculation shows a highly significant difference between the two series. We are, therefore, probably dealing not with a chance distribution, but with a real relationship between myopia and multiple sclerosis.

Investigating the relationship between refraction and the intermittent visual complaints, we find that of the 44 patients with visual complaints, 27, or 61%, were myopic; 13, or 30%, emmetropic, and 4, or 9%, hypermetropic.

Thus, almost two-thirds of the patients with intermittent visual complaints were myopic, whereas less than one-tenth were hypermetropic. This points to a relationship between myopia and a special type of multiple sclerosis characterized by intermittent visual complaints. As previously mentioned, the vision could be improved by concave lenses in three of the cases that exhibited visual impairment on heating.

As previously stated, the visual impairment is thought to be due to edema of the lens capsule. In this connection, the posterior lens capsule must be of particular importance, as alterations in this site—in the immediate vicinity of the optic center of the eye, where all rays pass—must entail maximum visual impairment upon minimum alteration in the index. In the endeavor to demonstrate an objective sign of the changes, one must look, therefore, for edema of the posterior lens capsule, e. g., by means of a slit lamp during the stress. A slit-lamp examination was performed on one patient who reacted to the heating by visual impairment. In this case edema seemed to arise in the posterior capsule. This finding, however, is not reliable enough to form the basis of conclusions.

SUMMARY AND CONCLUSION

In a fairly large group of patients with multiple sclerosis subjected to a standardized stress, the majority, or about 75%, showed aggravation of symptoms, in some cases even considerable. The exacerbation occurred within 10 to 15 minutes. After the experiment was stopped, most patients returned to the status quo within 15 to 20 minutes, while others required a somewhat longer readjustment.

The symptoms apparently comprise the entire nervous system, including the visual function. Certain findings indicate that the visual impairment at least is not merely a nervous phenomenon, but that far more peripheral tissue changes may contribute. It is possible, but not yet proved, that peripheral changes also play a role in eliciting the other symptoms. Such a peripheral factor cannot be ruled out primarily in the frequently marked adynamia, which sometimes may be accentuated to total paralysis and may be characterized by features reminding one of myasthenia, e. g., ptosis, bulbar symptoms, hypotonia, and loss of tendon reflexes. Since, however, other signs were unmistakably of "central" origin—appearance of the Babinski toe sign and spontaneous nystagmus—it must be presumed that the clinical phenomena represent a widespread action upon the entire organism.

Heating of the nature described is a "stress" on the multiple sclerosis organism. It is well known that many multiple sclerosis patients have observed such exacerbations upon varied forms of stress, not the least by heating. The patients often report this spontaneously. These spontaneous statements were the very reason why we decided to investigate this aspect. Infectious diseases also aggravate the condition of sclerosis patients. Perhaps fever is the most important factor other than phenomena of more complicated nature, such as allergization.

In the experiments, unlike natural stress of spontaneous occurrence, the stress could be regulated and interrupted. Therefore, it has exerted its action within an extremely limited period.

As is well known, the physiological reaction to stress is a complicated one. Many factors are involved. As regards heating, we know that heating is the immediate cause of vascular dilatation in the skin and in the central nervous system. The latter effect is known from a large number of animal experiments. Recently, Engel [3] demonstrated such vascular dilatation also in the nervous system of man. This is, of course, of particular interest in connection with the present investigation, because various workers have shown that the pathological changes in multiple sclerosis are of perivenous localization.† From the pathoanatomical point of view, multiple sclerosis is a kind of periphlebitis in which large plaques are formed by the confluence of numerous, small periphlebitic zones.‡ It has been shown also that in fresh zones the dilated vessels are surrounded by edema. Marius Haarr [6] (1951) has observed edema in the walls of the retinal vessels in multiple sclerosis.

The possibility of any development of edema in the parenchyma of the central nervous system must, however, be ruled out in the present experiments, considering that the symptoms subside in about 20 minutes. At any rate, such edema would have to be limited to the interstitial tissue. At the present time, it seems most reasonable to assume that an alteration takes place in the ion distribution in the membranes of the nervous system, of the eye, and possibly of the neuromuscular apparatus, with a corresponding alteration in the membrane potentials.

The preliminary result of the present investigation is the finding that a certain proportion of patients with multiple sclerosis exhibit intermittent visual impairment which does not seem to be related to alterations in the optic nerve function. This impairment is elicited particularly by physical exertion or heat and may be induced or reproduced by exposing the patients to a certain degree of heating. Patients with multiple sclerosis present an abnormally high incidence of myopia, differing significantly from that in a Danish normal series. Lastly, fluctuations in the visual acuity are far commoner in myopic than in emmetropic or hypermetropic subjects.

† References 4 and 7.

‡ References 4, 7, and 8.

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Evaluation of Carbon Dioxide Inhalation for Acute Focal Cerebral Infarction

CLARK H. MILLIKAN, M.D., Rochester, Minn.

The use of various methods of producing dilation of cerebral vessels as a treatment for cerebral infarction, hypertensive encephalopathy, or cerebral embolism has been reported. Russek and Zohman [1] have administered papaverine to patients with hypertensive encephalopathy. Cooper and Morello [2] injected the same drug into the carotid arteries after homolateral cerebral thrombosis. Furmanski * has treated "acute ischemia of the brain" with intravenous infusions of histamine diphosphate. Many reports have concerned the use of injections of procaine into the stellate ganglion following cerebral infarction and cerebral embolus. An incomplete list of these reports includes those of Naffziger and Adams,[5] Gilbert and de Takats,[6] Volpitto and Risteen,[7] Leriche,[8] Denny-Brown,[9] and Millikan, Lundy, and Smith.[10] All these attempts at treatment have theoretically one common property, the dilatation of cranial blood vessels inside and outside the cranial cavity.

Unfortunately, knowledge relating to the pathogenesis of acute focal cerebral infarction is so inadequate that there is no general agreement concerning the mechanism of development of the various types of cerebral infarcts. The role of vasospasm in this mechanism is disputed. Gilbert and de Takats [6] apparently considered vasospasm of great importance, while Adams and Vander Eecken [11] and Denny-Brown [9] contended that other mechanisms are more important. Pickering [12] emphasized that embolic phenomena associated with hypertension may produce many unexplained infarcts. The experiments of Corday, Rothenberg, and Putnam [13] indicated that transient relative hypotension may be an important factor in many instances. Gurdjian and Webster,[14] as well as Denny-Brown,[9] indicated that thrombosis of a carotid artery may be overlooked as the cause of a massive cerebral infarction. However, there is general agreement that around the portion of brain most severely damaged lies a zone of tissue, partially ischemic, which may potentially be restored to function if adequate circulation can be maintained or the existing blood supply supplemented by some therapeutic technique. The protection of this marginal zone has been the essential objective of most of the therapeutic efforts involving the use of vasodilating techniques.

The original development by Kety of the nitrous oxide technique for measuring cerebral blood flow has made possible the study in health and disease of methods theoretically capable of increasing the cerebral circulation. Of the numerous drugs studied, the inhalation of 5% carbon dioxide produces the greatest increase in cerebral blood flow. Kety and Schmidt,[15] Novack and associates [16] and Fazekas and co-workers [17] have reported an increase of 50% to 75% in cerebral blood flow during inhalation of this gas. The increase in the blood flow is smaller when subjects who supposedly have cerebral ar-

From the Sections of Neurology and Psychiatry, Mayo Clinic and Mayo Foundation.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

* References 3 and 4.

teriosclerosis inhale this gas; however, the increase is still a significant one. It has been demonstrated that this increase mainly results from decreased resistance of the cerebral vessels. The cerebral blood flow returns to the preinhalation level shortly after administration of carbon dioxide is discontinued. Novack and co-workers [16] reported that "in incipient or actual cardiac decompensation, inhalation of 5 per cent carbon dioxide has been found to embarrass further the general circulation and in many such instances to decrease the cerebral blood flow." Other than this, the danger of such therapy is slight.

Because the inhalation of 5% carbon dioxide consistently produces greater increase in cerebral blood flow than does cerebral vasodilatation by any other method, it was decided to study the possible effect of such "treatment" on the clinical course of patients with acute focal cerebral infarction.

SCOPE OF STUDY

Clinical observations on 275 patients encountered at the Mayo Clinic form the basis of this report. The method for making and recording these observations has been described previously.[10] The patients were all suffering from acute focal cerebral infarction, and a diagnosis of cerebral embolism was made in 26 instances. Standard methods were used for establishing the diagnosis, which was confirmed in 34 cases at necropsy. A group of 225 patients did not receive any medication thought to produce increased cerebral blood flow. This group forms a contrast group for comparison with the 50 patients who received inhalations of 5% carbon dioxide and 95% oxygen administered by means of a BLB mask. Inhalations of the mixture were given for 5 to 12 minutes during each hour for 48 hours after the onset of symptoms and then during the daytime for 5 additional days. As in preceding studies,† comparison of the two groups was made 14 days after the onset of symptoms, unless death of the patient occurred before that time. The ages of the patients who had infarction with and without cerebral embolism are shown in Tables 1 and 2. The incidence of hypertension and cardiac disease in

† References 10 through 18.

TABLE 1.—*Patients with Focal Cerebrovascular Disease: Contrast Group*

	Simple Infarction		Embolus	
Age, Yr.	Cases	Deaths	Cases	Deaths
30-39	9	0	5	3
40-49	23	1	1	0
50-59	47	3	8	4
60-69	69	10	5	1
70 or more	56	15	2	0
Total	204	29 (14%)	21	8 (38%)

TABLE 2.—*Patients with Focal Cerebrovascular Disease Treated with Carbon Dioxide*

	Simple Infarction		Embolus	
Age, Yr.	Cases	Deaths	Cases	Deaths
30-39	0	..	0	..
40-49	0	..	0	..
50-59	15	1	2	2
60-69	22	2	1	0
70 or more	8	2	2	2
Total	45	5 (11%)	5	4 (80%)

TABLE 3.—*Patients with Hypertension and Cardiac Disease*: Contrast Group*

Age, Yr.	Total	Hypertension	Cardiac Disease
30-39	14	10	6
40-49	24	16	3
50-59	55	39	8
60-69	74	53	15
70 or more	58	46	12
Total	225	164 (72%)	44 (20%)

* Some patients had both hypertension and cardiac disease.

TABLE 4.—*Patients with Hypertension and Cardiac Disease* Treated with Carbon Dioxide*

Age, Yr.	Total	Hypertension	Cardiac Disease
30-39	0	..	..
40-49	0	..	..
50-59	17	12	3
60-69	23	18	5
70 or more	10	9	4
Total	50	39 (78%)	12 (24%)

* Some patients had both hypertension and cardiac disease.

the 225 patients in the series who were not treated with inhalations of carbon dioxide and similar data for the 50 patients treated with the inhalations of carbon dioxide are shown in Tables 3 and 4.

COMPARISON OF RESULTS IN THE TWO GROUPS

The patients treated with carbon dioxide were concentrated in the sixth, seventh, and eighth decades of life, whereas a number of the patients who were not given carbon dioxide were in the fourth and fifth decades. Seventy-two per cent of the latter had hypertension, as contrasted with 78% of the patients receiving carbon dioxide. The percentage of patients with heart disease was greater in the treated group. The primary neurologic deficit initially present varied widely from patient to patient, but the percentage of patients having a similar amount of brain damage was essentially the same for the two groups. All of these factors indicate great similarity between the base-line group and the patients who were receiving carbon dioxide.

The residual neurologic motor defect present 14 days after cerebral infarction and the number of deaths of patients in each group are given in Tables 5 and 6. Emphasis has been placed on the residual motor defects rather than on the sensory phenomena because of the greater ease in objectively testing the former. Careful scrutiny of the data presented in Tables 5 and 6 reveals that 35% of the patients treated with carbon dioxide were normal or had varying degrees of monoparesis 14 days after onset of the infarction, whereas 16% of the contrast group were normal or had a relatively minor neurologic defect. The percentage of patients having residual hemiparesis of varying degrees was slightly greater for the patients not treated with carbon dioxide, but the mortality rate in the two groups was similar.

TABLE 5.—*Residual Neurologic Condition of 204 Patients in Contrast Group*

			Monoparesis				Hemiparesis				
Age, Yr.	Total	Normal	1	2	3	4	1	2	3	4	Died
30-39	9	3	..	..	..	..	1	..	5	..	..
40-49	23	4	..	..	1	..	2	7	4	4	1
50-59	47	7	..	..	1	..	7	6	20	3	3
60-69	69	7	3	1	..	..	11	11	7	19	10
70 or more	56	4	..	..	2	1	3	7	9	15	15
Total	204	25	3	1	4	1	24	31	45	41	29
Per cent of total	..	12+	←		4	→	12	15	22	20	14
Per cent of total: Summary					16				69		14

TABLE 6.—*Residual Neurologic Condition of Forty-Five Patients Treated with Carbon Dioxide*

			Monoparesis				Hemiparesis				
Age, Yr.	Total	Normal	1	2	3	4	1	2	3	4	Died
30-39	0	..	..	..	..	..	..	..	..	..	..
40-49	0	..	..	..	..	..	..	..	..	..	..
50-59	12	4	..	1	..	..	..	2	2	2	1
60-69	22	6	..	2	1	..	1	..	5	5	2
70 or more	11	..	..	..	2	..	..	5	..	2	2
Total	45	10	..	3	3	..	1	7	7	9	5
Per cent of total	..	22	←		13	→	2	16	16	20	11
Per cent of total: Summary					35				54		11

COMMENT

It has been previously emphasized ‡ that the natural history of cerebral infarction is

‡ References 10 through 18.

consistently inconsistent; that is, the course of the disorder varies greatly without any treatment. This natural variation in the position and extent of brain damage greatly increases the difficulty in accurately evaluating any new attempt at "treatment." It is for this reason that great care was used in collecting data concerning the contrast series of patients. The group of patients receiving carbon dioxide by inhalation is so small that no final conclusions are warranted concerning the efficacy of such therapy. In fact, the pathologic physiology of cerebral infarction is so poorly understood that it is not even known whether an increase in cerebral blood flow is desirable. That an increase in blood flow will actually deliver more oxygen to hypoxic brain in the marginal zone of a cerebral infarct has not been demonstrated. If increased concentrations of tissue carbon dioxide cause cerebral vasodilatation, maximal expansion of the vascular tree in the periphery of an infarct may already have taken place and inhalation of carbon dioxide would be of no value at all. These are problems which the present study does not in any way answer.

The favorable difference in the statistics herein reported for patients treated with carbon dioxide as contrasted with patients in the contrast group may represent an artifact which will disappear when a greater number of patients are treated and observed. From these observations it would seem that further study of the use of inhalations of carbon dioxide is indicated. Kety has commented that the increased cerebral blood flow associated with increased concentration of carbon dioxide in the blood is transient, disappearing a few minutes after the inhalation is discontinued. Perhaps a technique of administering the gas other than that described herein can be devised which will produce a more persistent increase in cerebral blood flow.

SUMMARY

Clinical observations concerning 275 patients with acute focal cerebral infarction encountered at the Mayo Clinic are reported. Of these 275 patients, 225 untreated, in the contrast group, did not receive any medication designed to produce increased blood flow in the cerebral vessels and 50 received carbon dioxide by inhalation. The technique for administering carbon dioxide by inhalation to such patients is described. The neurologic deficit present 14 days after infarction in the two groups of patients was compared. The results were slightly more favorable in the treated than in the contrast group. The treated group of patients is so small in number that no conclusions may be drawn from the study; however, more extensive investigation of the subject seems indicated.

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News and Comment

GENERAL NEWS

National Muscular Dystrophy Research Foundation Grant.—The National Muscular Dystrophy Research Foundation has made a $7,000 grant for the first year of a three-year research project to the Baylor College of Medicine, in Houston, Texas.

The study, which will be made by the Department of Internal Medicine, will deal with respiratory pigments in muscles. The scientists of the Department of Internal Medicine will first concern themselves with muscle tissues in normal animals and then attempt to find differences in tissues of animals who have a condition which resembles dystrophy. Later they will work with human patients.

In making the announcement of the grant, F. R. C. Brown, Foundation president, said the grant was made possible by those who have answered an appeal for funds made by Foundation poster boy, Raymond Waller, of Port Arthur. The youth, who weighs only 35 lb., began his appeal on his 18th birthday. He asked that everyone send 18¢ or $18 to Raymond in care of the Postmaster, Liberty, Texas.

"Raymond is an example to each of us," Mr. Brown said. "Despite the fact he is bedridden, he has been able to set up a campaign which may save youngsters of the future from the disease. I hope that thousands of other people will contribute to this campaign so we can reach our million-dollar goal and set up additional research projects."

Dr. Derek Denny-Brown, James Jackson Putnam Professor of Neurology at Harvard Medical School, heads the Foundation's Research Advisory Board, which approved the Baylor project.

The NMDRF was set up by two sisters, Sallie and Nadine Woods, both of whom are victims of the disease. TV star Ed Sullivan has joined the roster of Foundation national sponsors—U. S. Senator Price Daniel, Governor Allan Shivers, and Mr. and Mrs. Roy Rogers. Mrs. Dwight D. Eisenhower is national honorary president.

GENERAL NEWS

Veterans Administration Residencies in Psychiatry.—The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation, in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers, as well as an Annual Institute at the hospital. Training may commence at any time.

Psychic Functioning in Patients with Undiagnosed Somatic Symptoms

Clinical Evaluation

THEODORE LIPIN, M.D., New York

I. THE PSYCHIATRIC EXAMINATION: A DIAGNOSTIC TOOL

The psychiatric consultant on a neurological service is frequently called upon to aid in establishing the diagnosis of somatic symptoms when, after thorough study, the nature of the illness remains unclear. Perhaps the symptoms are related to psychopathology. The undiagnosed somatic symptoms may be of any type, including defects of motor and sensory functioning, involuntary movements, syndromes similar to those seen with brain tumors, states of disordered mental functioning akin to those occurring with epilepsy and narcolepsy, and various "atypical" or "bizarre" disturbances.

Psychiatric examination also is requested occasionally when a patient with an existing neurological or psychiatric illness develops new somatic symptoms or, after a period of stability, suffers from a progression of symptoms. The cause of the clinical change may be a newly developing illness, rather than a progression of the old illness.

A. Some Methods of Psychiatric Investigation.—Several methods, of varying reliability, are in use to obtain evidence of psychogenic illness.

One method, "diagnosis by exclusion," is particularly ineffective. The idea that a somatic symptom is related to psychopathology because medical studies fail to establish its "organic" nature is merely a hunch, alogically derived, frequently incorrect, and occasionally responsible for a medical tragedy.

Another technique, "longitudinal psychiatric anamnesis," is used to explore for a disturbing experience occurring just prior to the onset of the present illness. If this is found, and if the medical studies are negative, it is assumed that in some way the somatic symptoms are related to psychic processes.

Variants of this method are systematic investigation of the minutiae of the patient's sexual activity, with the mistaken idea that "good" or "bad" sexual functioning will correlate in some way with pertinent psychogenic factors; and the "common sense" approach, which focuses on the "reasonableness" and "insight" of the patient's conscious attitudes and thoughts, with the tacit, but erroneous, assumption that the more intelligent and cooperative the patient, the less likely the presence of a psychiatric disorder.

The impressions derived from these methods are based at best on conjecture and circumstantial evidence. They make little use, if any, of the psychiatrist's ability to examine current psychic functioning.

A third diagnostic approach, that of special psychological and clinical testing, assays the current status of various integrated ego functions by such procedures as the Wechsler-Bellevue Test; the Rorschach Test; the various figure, form, and field perception tests [1]; tests for the aphasias, and the clinical performance tests, such as those for detecting sensory extinction phenomena.[2] Their

From the Neurological Institute, Presbyterian Hospital.

attraction lies in their objective, clear-cut, repeatedly demonstrable results. They are of clinical help when the findings are definite and pertinent.

In actual practice, however, at times when diagnostic illumination is urgently needed, these tests often shed little or no light. They are more useful in demarcating the physiological sequelae of neural pathology.

B. Technique of Clinical Psychiatric Examination.—The psychiatrist, like the medical clinician, is not content merely with the history of the illness and the results of laboratory procedures. He performs an examination by scrutinizing, in the interview situation, the structure and functioning of the patient's psychic system. As the patient describes his condition, the psychiatrist observes the effect of the illness on thoughts, feelings, and actions. By following supposed "irrelevancies" and "digressions," purposely encouraged by his attitude of unselective attention, he learns about the affects and phantasies associated with the symptoms.

The psychiatrist is particularly attentive to the manifestations of unconscious impulses, defenses, affects, and phantasies, because only they can give rise to functional somatic symptoms.[3] Derivatives of these unconscious processes are expressed inadvertently during the interview in such forms as the sequence of association, the emphasis on or the avoidance of pertinent details, and the subtle fluctuations of mood, attitude, and behavior. Their expression is enhanced by allowing the patient to speak spontaneously, unfettered by the constricting demands of a concise, factual description of the medical history.

In this way the psychiatrist elicits signs much as the medical clinician auscultates for rales and percusses for dullness. Of particular diagnostic import are two findings: (1) The personality's response to experiencing the symptoms, and (2) the alterations in psychic functioning concomitant with the illness.

II. RESPONSE OF THE PSYCHE TO THE SOMATIC SYMPTOM: A DIAGNOSTIC SIGN

A symptom results when a lesion depresses or excites functioning, or so impairs a functional pattern that a more primitive pattern takes over. The pertinent problem for the psychiatric consultant is whether the lesion lies in the nervous or in the psychic system.

The end-effect of a lesion in either system may appear in a similar somatic form, such as pain, weakness, anesthesia, blindness, deafness, tic, tremor, or loss of balance. But the psychological or neurological dynamics generating the same symptom differ entirely from one another. A hemiplegia, for example, has one set of pathogenic (psychological) dynamics when caused by conversion hysteria and another set of pathogenic (neurological) dynamics when caused by a brain tumor.

A. The "Organic" Symptom: An Assault.—A lesion in the nervous system, in fact, a lesion in any organ system, lowers the preillness level of bodily functioning. The newly impaired functions are not available for psychic discharge and defense as fully as before. In this way the neural lesion also impairs psychic functioning.

The "organic" somatic symptom is perceived by the patient primarily as a noxious and frightening stimulus impinging from without the psyche. This "assault" fixes the patient's attention and provokes anxiety. Sometimes this primary anxiety is hidden from superficial view by a secondary affective state, such as depression, defiance, withdrawal, denial,[4] or mania, which is related to the patient's characterological reaction patterns. But careful examination elicits multiple signs of the marked anxiety that underlies and generates the secondary, "defensive" affect.

The patient, perceiving the symptom as an encroaching, often painful, threat to his integrity, seeks medical care in order to remove the "external" danger. With such motivation his efforts are centered on giving the doctor as much intelligence about the illness as is within his command. He describes his medical history spontaneously, with a pressure, interest, and concern that reflects both his anxiety and its fixation on the somatic illness.

Case 1 illustrates the psychic response of a "brain tumor suspect" to her "organic" ill-

ness. This woman had a serious lifelong neurosis, of which there was abundant clinical evidence. But the diagnostically important signs were that she (1) perceived her somatic symptoms as a new assault to her functional integrity and (2) reacted to them with anxiety. All her faculties were mobolized to remove the frightening symptoms of the present illness.

CASE 1 (P. H. #136696).—Miss K., a 35-year-old office worker, had noted intermittent suboccipital and cervical pain, lancinating in quality, for a period of three years prior to admission. Of late the pain and an associated "dizziness" became more intense and more frequent, appearing several times a day instead of several times a week. The attacks of pain, lasting one or two hours, were accompanied by marked anxiety and tremor and were relieved by lying prone. During the few months preceding hospitalization there was occasional, momentary diplopia on right lateral gaze. In recent weeks her stamina declined. Papilledema was detected for the first time three weeks prior to hospitalization.

On neurological examination no abnormalities were noted except for bilateral papilledema of 3 D. and bilateral occipital tenderness. Demineralization of the posterior clinoid processes and dorsum sellae, and displacement of the pineal shadow several millimeters downward and posteriorly were discerned on x-ray films of the skull. The outline of a lobulated mass occupying the region of the third ventricle was seen on ventriculographic films. Upon operation the diagnosis of a colloid cyst of the third ventricle was confirmed.

Psychiatric Examination.—This woman was first examined psychiatrically a few days after admission, before the results of the laboratory studies were known. In the history she gave were numerous allusions to and descriptions of symptoms related to chronic depression and anxiety, extending back to childhood. Her apathy and withdrawal seriously handicapped her heterosexual, social, and work relationships. Her mother had been institutionalized for 17 years because of "involutional melancholia."

Although she behaved during the interview as a passive, anxious, chronically depressed woman, suffering from a neurosis, it was equally clear that her spontaneous, pertinent, and informative description of her somatic symptomatology was given with grave concern and interest. Her neurotic symptoms were mentioned with the clear intention of giving the examiner a complete factual accounting, serving the purpose of accurate diagnosis, rather than that of gratification or reassurance by evoking the examiner's sympathy and guidance. She neither became engrossed with her personality problems nor sexualized, in any form, her relationship with the examiner. She behaved as a sick patient trying her utmost to give a doctor pertinent information. Her sole wish was to have the cause of her affliction removed. How else would she be able to carry on?

B. The "Functional" Symptom: a Defense.—A lesion in the psychic system, generating a somatic symptom, initially disrupts only psychic functioning. At first it produces only anxiety, tension, depression, or other psychiatric symptoms. If the psychopathology then progresses, primitive forms of restitution are activated to preserve and restore as much psychic functioning as is possible.

The "functional" symptom, a manifestation of such regression, serves a reparative purpose. Its inception ushers in a period of lessened agitation and disorganization. The internal, intrapsychic impulses responsible for the serious mental disruption are more painful and dangerous to the patient than the misery and impairment caused by the somatic defense.

The patient seeks medical care because he has somatic symptoms. He may hope that the somatic symptom is the cause of his anguish, and he may try to restrict his relationship with the doctor to the somatic disorder. But derivatives of his intense intrapsychic turmoil break through to appear clinically. In the interview the patient soon leaves the subsidiary subject of his somatic complaints in order to get on to the chief complaints: the fears, phantasies, and needs related to his anxiety. Herein lies his interest, his concern, and his wish for relief.

The "brain tumor suspect" in the following case responded to his illness as though it were a defense, and not an assault. He was concerned more about induction into the Army and guilt over "bad habits" than about his headaches. He had neither a brain tumor nor primary neural pathology.

CASE 2 (P. H. #136717).—Mr. S., an 18-year-old Negro high school graduate and office worker, noted progressively severer bilateral frontal headaches, sometimes throbbing and sometimes lancinating in quality, for a period of three weeks. He remained at home in bed because of the incapacitating nature of his head pains. Two weeks before hos-

pitalization he had fleeting spells of "dizziness," and during the two days before hospitalization he noted chest pain and neck stiffness. The past medical history was noncontributory.

No abnormalities (other than minimal bilateral papilledema) were noted on neurological examination. Cerebrospinal fluid pressure was 380 mm. of water; the protein content was 25 mg. per 100 cc.; the fluid contained no cells, and the test for syphilis was negative. Electroencephalogram, x-ray films of the skull, arteriogram, two pneumoencephalograms, ventriculogram, and sagittal sinogram were all within normal limits.

Because of the persistent papilledema, elevated cerebrospinal fluid pressure, and subsequent retinal hemorrhages, there was some threat to vision, and, therefore, to lower the cerebrospinal fluid pressure, a right subtemporal decompression was performed. About one week postoperatively the papilledema subsided and shortly thereafter disappeared. Repeated examinations during a follow-up period of nine months failed to elicit abnormal neurological findings. The patient was asymptomatic except for occasional mild headaches, "dizziness," and a subjective feeling of memory impairment. The diagnosis remained as idiopathic elevation of the cerebrospinal fluid pressure ("serous meningitis"). Cranioplasty was planned for the future.

Psychiatric Examination.—Mr. S. was examined psychiatrically a few days after his hospitalization, before any laboratory studies had been performed. He spoke of his illness in a friendly, but vague manner. The headaches, so incapacitating, were described poorly and reluctantly. He was unsure about the nature of the pain, its site, and its course. His first headache came when he had decided to quit his job because "it had no future."

His plans for a job interested him more than his headaches. With clarity and animation he spoke about his hopes for college. He had been offered an athletic scholarship because of his skill at basketball. But the Army stood in his way. Since his 18th birthday, several months before, he had a great fear of being drafted. His friends hated fighting in Korea; one had been killed. His wish for advice and guidance, perhaps even from the examiner, was quite clear.

When he was led back to his somatic symptoms, his former vagueness and dullness returned. He quickly left this uninteresting subject to relate with concern his ritualistic sleeping habits. He had a set posture when falling asleep and was alert to any change during the night. Lately this alertness had failed; he was disturbed to find himself in unexpected positions on awakening in the morning. This subject led to the evils of bad habits. He avoided "playing the numbers" and took laxatives for constipation.

At the end of the interview he seemed content to have reviewed his pressing concerns with a sympathetic listener. He did not return to his somatic complaints.

Interviews during the period of rigorous laboratory studies and after the craniotomy were remarkably similar to the initial interview. He referred briefly to his headaches and to the current procedures and then turned to more "interesting" subjects, his plans for college and job, and his sleeping habits.

Comment.—Serous meningitis causes very little disruption of neural functioning.[5] The psychic response to it, like that to a common headache, is less than the reaction to the profound disruption of a brain tumor. Such a differentiation is of clinical importance in "atypical" or "complicated" cases, such as Case 2, in which the strong suspicion of brain tumor was based on the papilledema and elevated cerebrospinal fluid pressure.

C. Limits to Diagnostic Value of Response to the Symptoms.—The focus of preoccupation on either somatic or psychic difficulties is a diagnostically reliable sign, only if, in the case of an acute illness, the patient is examined during the first three or four weeks, or if, in the case of a chronic illness with progressive pathology, the patient is examined during the first three or four years. At a later date the somatic symptoms become so utilized for defense, gratification, and secondary gain that the initial response to them erodes, changes, and loses its diagnostic usefulness.

Case 3, a woman with a 20-year history of seizures, illustrates the difficulties encountered when the examination is made late in the illness. This patient spoke of her mental lapses as though guilty over some secret, shameful, intimate activity, instead of objectively describing the effects of her meningioma. Because her illness now served to defend her from many painful, self-punitive impulses, it was perceived no longer as an assault.

Case 3 (P. H. #128724).—Mrs. O., a 56-year-old widow, noted momentary lapses of ability to speak, coming on once or twice a year for about 20 years. One day, two weeks prior to hospitalization, she had 10 such lapses. This sudden intensifi-

cation of her symptom, quite unique in her experience, troubled her sufficiently to seek medical advice. All her spells had been similar. They were characterized by a sudden loss of her ability to speak, lasting for a fraction of a minute, occasionally preceded by a vague sensation in her abdomen. During the seizure there was no subjective awareness of altered consciousness, loss of muscular power, involuntary movements, or altered sensory perception. She could hear and comprehend words spoken in her presence. Between attacks there were no disturbances referable to the nervous system.

Neurological examination of this right-handed woman was entirely normal except for the inconstant finding of a right homonymous hemianopsia. An electroencephalogram taken before hospitalization was said to contain evidence of a "left temporal focus," and one taken in the hospital recorded "almost continuous discharge of medium- to high-voltage, 15- to 20-per-second, spike activity, of a little higher amplitude on the right side. In addition, some slow wave activity was found in the two frontal areas." Cerebrospinal fluid pressure was 160 mm. of water; the protein content of the fluid was 642 mg. per 100 cc.; the fluid contained one white cell, and the Kolmer test for syphilis was negative. X-ray films of the skull were normal; there was no pineal shift. On pneumoencephalogram films there was "a marked lateral shift of the border of the third ventricle to the right. The body of the left ventricle has been displaced under the falx to the right of the midline (1.5 cm.)." An arteriogram contained evidence of an "expanding lesion, middle fossa, left." Craniotomy was performed, and a globoid, angioblastic meningioma, 12 by 10 by 8 cm. in size, was removed from the left sphenoid ridge.

Psychiatric Examination.—When interviewed, a few days after hospitalization, Mrs. O., a polite, apprehensive European lady, shied from giving the details of her illness. She filled the interview, obviously upsetting to her, by describing her experiences teaching elocution and giving public readings. She referred to her lapses only in connection with the embarrassment they would cause if they occurred while she was teaching or when on the stage. Her desire to terminate the interview was replaced every few minutes by a clutching request for reassurance that the forthcoming pneumoencephalogram would not harm her. Her concern and interest remained riveted to her personal problems. Her lapses seemed of minor importance.

There were no signs of mental confusion, intellectual impairment, or difficulty in grasping the abstract meaning of proverbs.

Comment.—In this case it was imperative to rule out a brain tumor not because of the psychiatric findings, but because of the seizure pattern. This is an example of how experience in neurology enables the consultant to place all the medical data in proper perspective.

III. ALTERATIONS IN PSYCHIC FUNCTIONING: A DIAGNOSTIC SIGN

A. Psychic Disturbances with Lesions in the Central Nervous System.—A lesion in the central nervous system impairs psychic functioning because it impairs neural functioning.

1. Gross Neurological Signs: If there are gross neurological signs, such as paralysis, reflex changes, incoordination, dysesthesia, aphasia, or mental clouding, psychiatric examination usually has no diagnostic purpose. Yet, if such an examination were made, one would detect the psychiatric signs of the brain pathology. When the lesion is large, there is some impairment of judgment, insight, behavior, memory, or orientation, similar to that found in organic psychosis.

The following case illustrates the rather blatant abnormality in judgment and behavior observed in a man whose memory, orientation, and communication ability were intact. He had a large astrocytoma.

CASE 4 (B. C. H. #1178224).—Mr. S., 31 years old, was admitted to the Boston City Hospital with a five-year history of grand mal seizures, poorly controlled of late, and of a one-month history of headaches, nausea, vomiting, and mild weakness of his left arm.

Neurological examination revealed mild left-sided hemiparesis; slight left-sided facial weakness; hypoactive deep tendon reflexes, more so on the left; extensor Babinski response on the left; slight ataxia, and blurring of the right optic disc margin. Cerebrospinal fluid pressure was 250 mm. of water, and the protein content was 34 mg. per 100 cc.

While studies were being completed, preparatory to craniotomy, the patient suddenly became comatose and died. An astrocytoma of the right frontal lobe, infiltrating almost all of the right cerebral hemisphere, and herniation of the brain through the tentorium were visualized at autopsy.

Psychiatric Examination.—The patient's attitude varied from facetious compliance to irritable negativism, entirely inappropriate to the circumstances of his illness and hospitalization. He knew where he

was, and those historical facts which he offered were accurate. He wanted to be left alone in his bed and sleep. But when he was approached and contacted despite his withdrawal, irritability, and uncommunicativeness, he spoke only about his current symptoms. This pertinence was not disturbed by signs of gross confusion or psychopathological phantasies.

Comment.—When, as in Case 4, the intracranial tumor is intrinsic to the brain, the psychiatric signs of brain pathology remain evident regardless of the duration of the illness. But when, as in Case 3, the intracranial tumor is extrinsic to the brain, the impairment of neural and psychic functioning may be milder, so that after a few years the psychiatric signs of organic pathology fade away.

2. Absence of Neurological Signs: When the lesion is small or in a "silent" area, and not accompanied by neurological signs, subtle alterations in psychic function due to it may be detected by psychiatric examination. Slight psychic impairments, taking a myriad of forms, often lead to a hesitation in the speed and integration of perceptions, conceptions, or actions, so that there is a degradation of the more complex psychic activities.

The psyche's initial perception of this impaired functioning, coming on long before there are overt neurological signs, is not a conscious awareness that there is a disorder. Instead, a vague uneasiness appears, followed by increasing fatigue and difficulty with exacting work. It becomes harder to conceptualize, or remember, or react promptly, or organize one's thoughts, or perceive subtle sensations, or perform delicate motor acts. Gradually the patient senses that some noxious influence impairs the previous quality of performance.

An automatic, unconscious strengthening of the psychic defense mechanisms often takes place to overcome, deny, and compensate for the impairment. For example, as K. Goldstein and others have shown, some patients with brain lesions attempt to cope with their confusion and disorganized mental functioning by ritualistic, obsessive-compulsive behavior. They withdraw from relationships that require more psychic intactness than they have, and they favor the more easily grasped, concrete, literal thinking, in preference to abstract thinking. They resort to regressed and to psychopathological patterns in coping with the anxiety and incapacitation caused by the illness.

B. Psychic Disturbances with Acute Conversion Symptoms.—All areas of psychic functioning are disturbed during the three or four weeks following the onset of a major conversion symptom, such as hemiplegia, hemianesthesia, blindness, deafness, generalized dyskinesia, or impaired mentation similar to that found with psychomotor epilepsy, narcolepsy, cataplexy, and encephalitis. During this period the patient appears dazed; experiences feelings of dissociation, depersonalization, and detachment from reality, and has a derangement of memory and affect, regardless of whether the primary diagnosis is neurosis or psychosis. The bland, dreamy-eyed façade, covering intense agitations and anxieties, may be disrupted for short periods by panic, weeping, screaming, or thrashing.

The intense psychic crisis and upheaval concomitant with and necessary for the development and emergence of a severe conversion symptom usually subsides within a month and the personality regains its organization. *La belle indifférence is* noted then only when the patient speaks of residual somatic symptoms.

The next case illustrates the dissociation and amnesia that accompany an acute hysterical hemiplegia. During the course of a week, with therapy, the gross mental disturbance subsided and disappeared hand in hand with the paralysis. Weeks later, during further psychiatric investigation, the underlying illness was proved to be schizophrenia, as is the case so often when there are massive conversion symptoms.

CASE 5 (P. H. #064309).—Miss V., a well-developed 16-year-old college freshman, was hospitalized because of a flaccid paralysis of her right upper and lower extremities, headache, and a partial amnesia for the preceding five days. Five days before admission, while sleeping at the college dormitory, she awoke in panic from a nightmare, fell out

of bed, "lost consciousness," and "awoke" some hours later, noting a severe suboccipital headache. Two days later weakness of the right arm developed. Associated with this were drowsiness, difficulty in following conversations, decreased visual acuity of her right eye, ringing in her ears, and nausea. Shortly thereafter her right lower extremity became paralyzed.

No abnormalities were noted on neurological examination other than a fluctuating ability to move her right extremities, which were flaccid, and a variable loss to all sensory modalities over an area from C2 to T9 on the right and over the entire right lower extremity. Deep tendon reflexes were normal. X-ray films of the skull, cerebrospinal fluid examination, and an electroencephalogram were all normal. Her somatic symptoms, diagnosed as conversion hysteria, disappeared in the course of a week, while she was receiving psychiatric therapy.

She was then transferred to the Psychiatric Institute for further study of the underlying psychiatric disorder. While there, before returning to her college work, several months later, she became quite agitated for several weeks, during which she had auditory hallucinations and exhibited self-destructive behavior. Her discharge diagnosis was catatonic schizophrenia.

Psychiatric Examination.—Miss V. was interviewed initially three days after hospitalization, and eight days after the onset of the paralysis. Lying immobile in her bed, she opened her eyes when spoken to and slowly answered questions about her illness in a vague, fragmented, dazed manner. "I became paralyzed while at college and they brought me here by ambulance." She was detached from the history she told and from the doctor she addressed. When she was questioned for specific details, there were many lacunae in her memory. Some isolated facts were recalled only after a tense momentary hesitation. Her daze persisted throughout the day's activities.

During subsequent daily interviews, directed toward removing the amnesia, intense feelings of anxiety and guilt momentarily replaced her detachment whenever she recovered fragmentary recollections of her relationship with a college girl friend. As her memory revived, her dissociation and hemiplegia subsided. Within a week she had regained much of her customary spontaneity and warmth. She would have returned to home and college had she not been advised to undergo further investigation.

When there are no signs of major psychic decompensation during the first three or four weeks of severe somatic symptoms, these are not likely to be conversions.

In the following case, a hemiplegia, due to a ruptured intracranial aneurysm, developed in a woman with a hysterical character structure. Acute concern over her paralysis, reaching out for help, and absence of dazed detachment, three signs consistent with somatic pathology, were of greater diagnostic importance than the manifestations of her chronic neurosis.

CASE 6 (P. H. #1110264).—Five days prior to admission to the Neurological Institute, Mrs. M., a 42-year-old mother, developed a severe occipital headache following a bout of coughing. Several hours later she was found comatose. When examined at a local hospital, shortly after, she was semistuporous, had a stiff neck, and on each of four lumbar punctures was found to have bloody spinal fluid. Five days later, at the time of admission to the Neurological Institute, she was semistuporous, restless, retching, and moaning and had a stiff neck. The next day she developed flaccid hemiplegia, facial palsy, and hypesthesia to every sensory modality, all on the right side. Deep tendon reflexes were normal. There was no Babinski sign.

Seventeen years before, following an appendectomy, Mrs. M. had a right-sided hemiparesis, which gradually disappeared in the course of a few weeks. Five years before, for a period of a week, she had several "black-out" spells, during which she remained unresponsive for a fraction of an hour. Six months before, for a period of a few days, she noted that at times "things looked different when seen with one eye than with the other."

Cerebrospinal fluid pressure was 60 mm. of water; its color was xanthochromic, and its protein content was 576 mg. per 100 cc. X-ray films of the skull, the arteriogram, and the electroencephalogram were within normal limits. No porphyrins were found in the urine.

During the next two weeks her mental status cleared, but the almost total hemiplegia persisted unchanged. As she regained her orientation and memory and established contacts with others, she revealed herself as a demanding, irritable, facetious, sarcastic woman, who acted out her feelings. At times when her doctor handed her a glass of water or a cigarette, at her request, she suddenly became agitated, complained that her tongue was swelling, started retching, dropped back on to her bed in a swoon, and remained unresponsive for a minute. A few minutes later, following a period of bewilderment, she resumed her appropriate contact with her surroundings and continued the conversation with her doctor with proper affect and coherence.

The impression in the minds of some that her paralysis was hysterical was strengthened when she

developed a transient flaccid paralysis of the left lower extremity after being hypnotized, in an unsuccessful attempt to remove the original paralysis.

Psychiatric Examination.—Mrs. M., a thin, pale, drowsy woman, whose right arm and leg lay flaccid and immobile, and whose facial expressions were dampened on the right, was interviewed three weeks after admission. She was depressed and concerned about her paralysis and its effect on her ability to care for her two young children. A burning question for her was whether her strength would return to her limbs. Would the doctor not reassure her? Mrs. M. was frightened by her disability and reached out for help. Her neurotic impulses, such as the need to sexualize relationships, were of secondary interest to her.

Follow-Up.—Nine months later, when the patient was discharged from the Psychiatric Institute, where she had been sent for further study, the total hemiplegia and facial paresis were unimproved. The flaccid muscles of the right limbs were grossly atrophic. The patellar reflex was more active on the right, but other deep tendon reflexes were equal on the two sides. There was no Babinski sign. Psychological tests elicited evidence of organic cerebral disorder.

IV. SOMATIC MEMORY: A CAUSE OF SOMATIC SYMPTOMS

Pains and bodily sensations, often strikingly similar to the symptoms of organic syndromes, may not be due to somatic or hysterical illness. They may be memories, expressed somatically, rather than mentally. "To recall," in this primitive, preconceptual form of memory, is to reexperience the bodily sensations felt during the original event.

The somatic symptoms experienced during a forgotten childhood illness sometimes reappear when the old illness becomes associated with current experiences. The recurring sensations are usually so transient and mild that a doctor is not consulted, but in some circumstances they are sufficiently intense to comprise the "chief complaint." Medical studies are normal unless the childhood illness left permanent scars or sequelae.

The anxiety over the symptom also recurs but is attenuated in comparison with the concern felt with the original illness. Psychic functioning remains intact, in contrast to the gross decompensation occurring with acute, massive conversion symptoms.

"Somatic memory" can be diagnosed with confidence only after prolonged psychiatric study. Remembering the existence of such a syndrome will lead to greater caution in diagnosing "conversion hysteria."

Clinical Example.—A 33-year-old man, undergoing psychoanalysis, noted the onset of a constant, dull ache, radiating from the 12th thoracic vertebra to the left lower quadrant of the abdomen, and a similar ache along the anteromedial margin of the left lower rib cage. He could not remember ever having had similar symptoms.

Associations during his analytic hours at this time were related to experiences when he was 3 years old. Gradually, memories of a severe injury to the spine and ribs were retrieved from his amnesia. As fragments of the episode were recovered, the pain lessened and disappeared, only to recur for hours or days in subsequent weeks and months whenever further ramifications of the experience came to light.

Thorough physical examination was normal except for a slight scoliosis and a slight shortening of the right lower extremity. On x-ray films, extensive old fractures of the 12th thoracic vertebra and of the costochondral margins of the 9th, 10th, and 11th ribs were noted.

SUMMARY

Some psychiatric methods used to determine whether psychic factors are contributing to the presence of somatic symptoms are discussed.

A technique of clinical psychiatric examination is described that gives information about the unconscious response to the somatic symptom, and the alterations in psychic functioning concomitant with the disease. Such findings are more reliable for diagnosis than the anamnesis alone.

These findings are diagnostically useful only when the examination is performed during the first phase of the illness, when the pathology is active and the initial psychic response is unmodified by integrative and adaptive processes.

Somatic symptoms due to acute somatic pathology are felt as "assaults." Somatic symptoms due to acute psychic pathology are responded to as though they were "defenses"; most of the interest and concern centers instead on other anxieties.

Alterations in psychic functioning, present with all neural pathology, may be detected by

psychiatric examination before the appearance of neurological signs or overt somatic symptoms.

A state of profound psychic disorganization is present early in the course of major conversion symptoms. The absence of dissociation and amnesia comprises formidable evidence against the diagnosis of acute hysteria.

Pains and other bodily sensations similar to those occurring with somatic illness may be "somatic memories." Patients with this syndrome have no signs of organic disease or of gross psychic decompensation.

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Intravenous Hydrocortisone, Corticotropin and the Electroencephalogram

GILBERT H. GLASER, M.D.
DONALD S. KORNFELD, M.D.
and
ROBERT P. KNIGHT Jr., M.D., New Haven, Conn.

Evidence continues to accumulate concerning a relationship between the adrenal-hypophyseal axis and central nervous system functioning, and this has been reviewed recently.* Clinically, the observation of patients with hyperadrenal states occurring naturally or induced by corticotropin (ACTH) and cortisone reveals occasional central nervous system aberrations manifested by nonspecific organic psychotic reactions, electroencephalographic abnormalities, and convulsions. The incidence of these reactions is unpredictable, however. For example, prolonged administration of corticotropin and cortisone has been found to produce significant alterations in the electroencephalogram in certain series † but less so in others.‡ Similarly, observations on epileptic patients have been contradictory. These hormones induced an increase in electroencephalographic abnormality and no effect on seizures in one series,[9] but a reduced incidence of seizures associated with an improvement in the electroencephalogram in another group.[10] However, in a series of controlled experiments using the electroshock threshold of rats, Woodbury§ has demonstrated that cerebral excitability may be increased by cortisone and decreased by desoxycorticosterone. Corticotropin did not produce a significant change when administered alone but did lower a threshold raised by desoxycorticosterone. Torda and Wolff[13] found that prolonged administration of corticotropin in rats induced a decreased cerebral excitability to pentylenetetrazol, but in acute experiments with single or repeated injections of corticotropin an increased electrical activity of brain appeared, with spiking, paroxysmal discharges and increased excitability. Also, Costa and Bonnycastle[14] demonstrated that corticotropin and cortisone increased, and desoxycorticosterone decreased, the susceptibility to "Agene-induced" convulsions in dogs.

Hydrocortisone (Compound F) has been prepared recently for intravenous administration. This hormone is similar to cortisone in its qualitative effects but is estimated to be approximately twice as potent.[15] This preparation therefore provided an opportunity to observe acute effects on the electroencephalogram of a pure highly potent steroid in high concentration. There have been no previous observations on the effects of the acute administration of corticotropin or hydrocortisone on the electroencephalogram of humans. The present investigation contrasts the effects of these two hormones during acute intravenous administration on two groups of subjects: epileptic and nonepileptic.

MATERIALS AND METHODS

Fourteen subjects were studied (Tables 1 and 2). Nine of these had a past history of seizures (grand

From the Section of Neurology, Department of Internal Medicine, Yale University School of Medicine.

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† References 3, 4, and 5.

‡ References 6 through 8.

§ References 10 and 12.

mal or psychomotor), while five were without any previous history of a convulsive episode. The electroencephalograms were recorded with standard Grass Model III equipment (eight channels). Sixteen electrodes were utilized in four bipolar runs; (1) right and left parasagittal; (2) anterior coronal and midcoronal; (3) midcoronal and posterior coronal, and (4) bilateral temporal and frontal. A three-minute period of hyperventilation followed each regular run, and photic stimulation was administered to the seven subjects given hydrocortisone. Recordings were made prior to the intravenous infusion and then at approximately two-hour intervals until all of the material was administered. The patients receiving corticotropin were given 25 mg. of the standard Armour preparation in 500 cc. of isotonic saline over a four-hour period. In five of the seven cases so studied 25 mg. was also administered intramuscularly at the time the infusion was started.

The hydrocortisone was provided as 100 mg. in 500 cc. of a solution of 5% dextrose and 1% ethanol.‖ It also was administered intravenously over a four-hour period. During this time venous blood and urine samples were obtained at two and four hours for analysis of electrolytes. Standard flame photometric methods were used for the determination of sodium and potassium, and the thiocyanate titration method was used for chlorides.

Total eosinophile counts were performed on 13 patients just prior to the initial venipuncture and again when the infusion was terminated, at four hours.

The encephalograms were evaluated by visual inspection and by a method of frequency spectrum analysis.[17] Right parietal and left frontotemporal runs were analyzed in each record. Frequencies more rapid than 13 c/sec. were classified as low voltage fast (L. V. F.). For convenience in charting, as in Figure 1, the relatively small quantity of 5 c/sec. activity was tabulated in the 6 c/sec. column.

TABLE 1.—*Electroencephalographic Changes with Intravenous Corticotropin*

Patient	Age, Yr.	Sex	Clinical Diagnosis	Medical Therapy	Corticotropin Administered	Control EEG	EEG Changes During Corticotropin I. V.
I. J.	49	F	Rheumatoid arthritis	Acetyl salicylic acid, 3 gm/day	25 mg. I. V.	Normal 10 c/sec. and low-voltage fast	Intermittent random 5-7 c/sec. in small amounts
A. B.	22	F	Rheumatoid arthritis	Cortisone 37.5 mg/day; KCl 1.8 gm/day	25 mg. I. V.	Normal 10-12 c/sec. and low-voltage fast	Alpha shift to 8-9 c/sec.; intermittent random 5-7 c/sec. in small amounts (Fig. 1)
A. C.	48	F	Progressive muscular dystrophy	None	25 mg. I. V. 25 mg. I. M.	Normal low-voltage fast	No significant change
D. K.	29	F	Epilepsy, psychomotor	None	25 mg. I. V. 25 mg. I. M.	Abnormal: 9-10 c/sec., 5-7 c/sec., and 4-5 c/sec., diffuse	Slight increase in 4-5 c/sec., alpha shift to 8 c/sec.
J. T.	32	F	Epilepsy, psychomotor	Dilantin 0.3 gm/day; phenobarbital 0.06 gm/day	25 mg. I. V. 25 mg. I. M.	Abnormal: 8-10 c/sec., 5-7 c/sec., and 3-4 c/sec. bursts, diffuse	Moderate increase in 5-7 c/sec. alpha shift to 8 c/sec. (Fig. 2)
J. P.	44	M	Epilepsy, grand mal	Dilantin 0.6 gm/day; phenobarbital 0.12 gm/day	25 mg. I. V. 25 mg. I. M.	Abnormal: 9-10 c/sec., 5-7 c/sec., diffuse	No significant change
L. B.	53	F	Epilepsy, psychomotor	Dilantin 0.3 gm/day; phenobarbital 0.03 gm/day	25 mg. I. M. 25 mg. I. V.	Abnormal: 9-10 c/sec., 5-7 c/sec., diffuse	No significant change

RESULTS

Effects of Intravenous Corticotropin (Table 1).—Four epileptic and three nonepileptic patients were studied in this group. The spectrum analysis showed in three instances (two epileptics and one nonepileptic) merely a slight shift in the dominant alpha rhythm to a slower, but still normal, frequency. The other two epileptic subjects showed essentially no change. Certain significant alterations occurred in the frequency spectrum of a 23-year-old rheumatoid arthritic (A. B.). This patient had been receiving cortisone for approximately one year at a dosage level of 75 to 100 mg. a day. The changes in the electroencephalogram are shown in Figure 1.

‖ The hydrocortisone preparation was supplied by Merck & Company, Inc., courtesy of Dr. Elmer Alpert. It is doubtful whether the 1% ethanol in the vehicle affected the electroencephalogram to any significant degree. The rate of administration was such that the calculated maximum accumulation in the average subject after the first hour could be only 2.5 mg. per 100 gm. It has been shown that ethanol is metabolized at the rate of 10 to 25 mg. per 100 cc. per hour.[16]

TABLE 2.—*Electroencephalographic Changes with Intravenous Hydrocortisone*

Patient	Age, Yr.	Sex	Clinical Diagnosis	Medical Therapy	Hydrocortisone Administered	Control EEG	EEG Changes During Hydrocortisone I. V.
D. S. K.	24	M	Normal, medical student	None	60 mg. I. V.	Normal, 10-11 c/sec.	Alpha shift to 8-9 c/sec.
R. K.	24	M	Normal, medical student	None	100 mg. I. V.	Normal, 12-13 c/sec. and low-voltage fast	No significant change
S. B.	24	M	Craniopharyngioma, postoperative; epilepsy, grand mal	Dilantin, 0.3 gm/day	90 mg. I. V.	Abnormal: mixed 8-10 c/sec., 5-7 c/sec., and bursts of 2-3 c/sec. spike-wave	Moderate increase in 5-7 c/sec. and 2-3 c/sec. spike-wave activity
H. S.	20	M	Epilepsy, psychomotor	Mesantoin, 0.6 gm/day; Tridione, 0.9 gm/day	100 mg. I. V.	Abnormal: random 5-7 c/sec. and low-voltage fast	Moderate increase in 5-7 c/sec.
M. R.	22	M	Epilepsy, psychomotor, grand mal	Dilantin, 0.5 gm/day; Mesantoin, 0.1 gm/day	100 mg. I. V.	Abnormal: mixed 8-10 c/sec., 5-7 c/sec., and 4-5 c/sec.	Slight increase in background 5-7 c/sec.
A. A. B.	18	M	Epilepsy, grand mal	Dilantin, 0.3 gm/day	53 mg. I. V.	Abnormal: mixed 8-10 c/sec., 5-7 c/sec.	Alpha shift to 8 c/sec.; slight increase in 5-7 c/sec.; appearance of 4-5 c/sec.
G. A.	24	F	Epilepsy, grand mal	Phenobarbital, 0.48 gm/day	55 mg. I. V.	Abnormal: mixed 10-12 c/sec., 5-7 c/sec., and 3-4 c/sec. bursts and occasional 2-3 c/sec. spike-wave bursts	Marked increase in incidence and duration of 2-3 c/sec. spike-wave bursts (Fig. 3)

Shifts to a slower dominant alpha rhythm occurred at two hours, and, in addition, 6 to 7 c/sec. activity appeared. In the final recordings, taken one and a half hours after the infusion, there was a suggestion of a tendency toward a return of the faster frequencies originally present.

An over-all visual inspection of these records, however, gave the general impression that in four instances (I. F., A. B., D. K., and J. T.) there was an increase in the occurrence of random, diffuse, but intermittent 5 to 7 c/sec., or theta, activity. This type of change is shown in Figure 2 and was somewhat greater in the two epileptic subjects (D. K. and J. T.), with previously abnormal electroencephalograms, than in the nonepileptics (I. J. and A. B.).

Effects of Intravenous Hydrocortisone (Table 2).—Seven subjects were studied in this group: Five of these were patients with a past history of seizures, and two were medical students with no history of a convulsive episode. The frequency spectrum analysis demonstrated only slight changes, which were inconstant and not considered significant, except for two instances of alpha shift to a slower dominant frequency (D. S. K. and A. A. B.). However, the over-all evaluation of the records of the five epileptic subjects showed that there were alterations induced in the basic patterns. In four cases an increase in the 5 to 7 c/sec., or theta, activity occurred. This change was particularly prominent in three instances (S. P., H. S., and G. S.). The record of one epileptic patient (G. A.) is shown in Figure 3. Prior to the intravenous administration of hydrocortisone, infrequent atypical 2 to 3 c/sec. spike-wave activity was present. However, during the hormone administration a marked increase in this spike-wave activity occurred, so that it became almost continuous. This type of prolonged seizure discharge had

TABLE 3.—*Serum Electrolyte Changes During Intravenous Hydrocortisone*

	Sodium*			Potassium*			Chloride*		
Patient	0 Hr.	2 Hr.	4 Hr.	0 Hr.	2 Hr.	4 Hr.	0 Hr.	2 Hr.	4 Hr.
D. S. K.	137.1	139.8	139.6	3.22	3.50	3.90	96.50	96.00	97.50
R. K.	139.0	141.0	143.0	3.1	3.5	3.7	104.0	102.5	100.6
S. B.	139.5	138.0	137.8	3.9	3.9	3.7	101.3	101.5	101.7
H. S.	146.3	143.8	145.4	3.55	3.96	4.30	102.3	101.4	101.7
M. R.	140.0	141.1	141.5	3.75	3.75	4.00	96.10	94.50	94.00
A. A. B.	140.8	140.6	142.2	3.35	3.53	4.44	102.0	101.5	102.3
G. A.	136.7	135.0	135.0	3.7	4.3	4.2	97.5	97.7	97.5

* Values are expressed as milliequivalents per liter of serum.

never appeared in her previous electroencephalograms. A similar, but less marked, increase in spike-wave discharges occurred in the record of S. B.

Photic stimulation did not produce any significant changes at any time, either during the control runs or during hydrocortisone administration.

Sodium, potassium, and chloride concentrations were determined in the serum and urine samples from the subjects receiving hydrocortisone. These data are presented in Table 3. There were no significant alterations in serum and urine sodium or chloride concentrations. However, a significant rise in serum and urine potassium occurred.

The total eosinophile count was employed as a test of adrenal steroid activity in 13 patients (all but L. B.). In every case, with the exception of A. B., after corticotropin or hydrocortisone there was a greater than 50% fall in total eosinophiles by the fourth hour. In Patient A. B. the initial count of 200 changed only to 178 four hours after the corticotropin was started. This patient's adrenal cortex was regarded as unresponsive, a situation probably related to the exogenous cortisone administration (see above).

COMMENT

Information obtained from this investigation indicates that the intravenous administration of hydrocortisone and corticotropin may exert effects upon the electrical activity of the cerebral cortex, as determined by the electroencephalogram. These changes are somewhat inconstant, but it may be stated that a trend was observed for the increased appearance of random, diffuse 5 to 7 c/sec. or theta, activity. This occurred more frequently in the electroencephalograms of the epileptic patients, and in two instances there was an increase in the intensity of seizure discharges in the electroencephalogram. No actual clinical seizures were induced, however. Also, the effect of the hydrocortisone was more definite than that of the corticotropin.

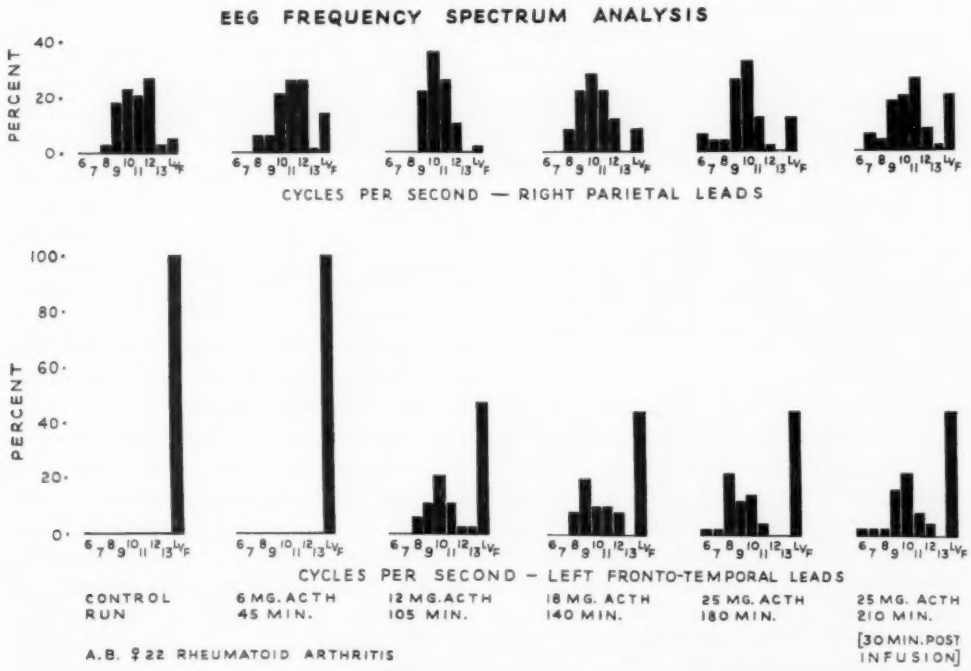

Fig. 1.—EEG frequency spectrum analysis of Patient A. B. The later recordings demonstrate a shift in the dominant alpha rhythm toward slower frequencies, while 6- to 7-c/sec. activities appear for the first time.

The less striking effect of corticotropin could be due to its relatively delayed action, and in this investigation this study was carried on for only four hours. In addition, the effect of corticotropin upon the adrenal gland itself is nonspecific. Actually, this hormone stimulates the adrenal gland to produce both cortisone-like and desoxycorticosterone-like hormones. Since cortisone and desoxycorticosterone exert antagonistic effects upon cerebral excitability,¶ it is possible that a similar neutralizing situation occurs with the

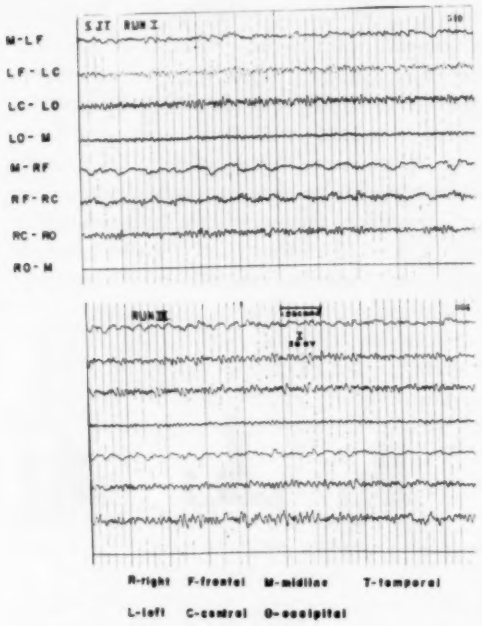

Fig. 2.—EEG of Patient J. T. There is a higher incidence of background 5- to 7-c/sec. activities in Run III, performed just after the infusion of corticotropin was completed.

mixed adrenal hormone output induced during acute corticotropin administration. However, the effect of corticotropin on the electroencephalogram of Patient A. B. (Fig. 1) is of interest. Since this patient had received cortisone therapy for one year, she was regarded as having a functionally suppressed adrenal cortex. In this instance the effect of the corticotropin on the electroencephalogram, a definite production of theta activity, may have been independent of adrenal stimulation and might be indicative of a direct effect on the cerebrum. This has been suggested by Torda and Wolff,[13] who demonstrated an increase in cerebral excitability and electroencephalographic abnormalities after the acute administration of corticotropin in adrenalectomized rats. It also is conceivable that the electroencephalographic abnormalities present in patients with Addison's disease may be a function of high serum adrenocortical hormone [18] rather than low steroid levels.

The increased susceptibility of epileptics which is suggested by this study is compatible with the reports of spontaneous seizures occurring in otherwise nonepileptic subjects receiving adrenal steroid therapy.#

The mechanism of these changes remains obscure. Many studies have been undertaken in an effort to correlate the known effects of these hormones on somatic metabolism and electrolyte balances with changes in the central nervous system. The relevant data have been reviewed recently * and may be summarized as follows: Intracellular electrolyte concentrations in the brain are apparently independent of marked changes of serum concentrations, but the excitability of the cerebral cortex varies inversely with the serum sodium, and directly with brain sodium concentrations. Also, it has been found that the adrenal steroids produce no significant changes in cerebral blood flow or carbohydrate metabolism with therapeutic dosage levels. Woodbury [12] concluded that cortisone and related oxysteroids act upon brain excitability without influencing brain or plasma electrolytes.

A detailed report of the observations in this present series of the serum and urine electrolytes is being made elsewhere.[23] The significant changes were the increases in serum and urine potassium concentrations in the four-hour period of hydrocortisone administration. The degree of change in the electroencephalogram was quite independ-

¶ References 11 and 12.

References 19 through 22.

* References 2 and 12.

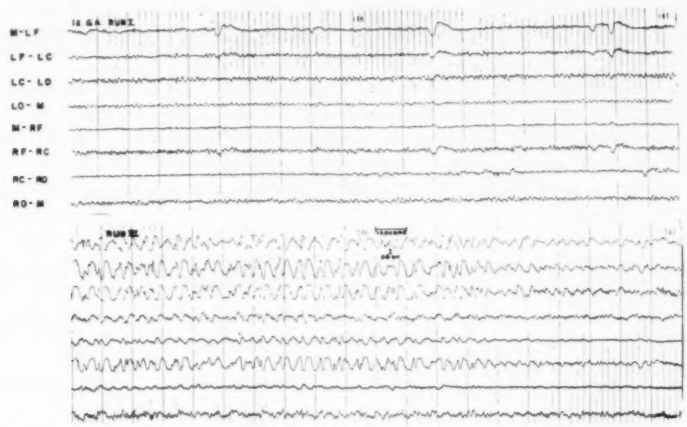

Fig. 3.—EEG of Patient G. A. There is an increase in the incidence and duration of 2- to 3-c/sec. slow wave and spike-wave discharges in Run III, just after the infusion of hydrocortisone was completed.

ent of the alterations in potassium concentrations. While shifts in the sodium, potassium, and chloride concentrations of brain and its extracellular fluid may be involved in changes in cerebral electrical activity, this is not always the case, and the detection of specific variations by gross methods, such as serum analysis, is not applicable. Further direct investigations of the electrolyte distributions and shifts within brain substance itself are indicated.

The significance of these hormonally induced changes in the electroencephalogram with regard to cerebral functioning is not clear. There has not been any definite correlation with the abnormal mental states appearing in certain instances.[3] However, the type of electroencephalographic alteration, usually an increase in theta activity or bilateral spike-wave discharge, has suggested that there may be a direct effect of these hormones on the deeper, subcortical diencephalic structures.[4]

SUMMARY

The intravenous administration of both corticotropin and hydrocortisone may induce an increase in theta activity (5 to 7 c/sec.) in the electroencephalogram, although hydrocortisone would seem to exert this effect more consistently and to a greater degree than does corticotropin.

The effect was somewhat greater in epileptic subjects with previously abnormal electroencephalograms. In two instances hydrocortisone produced an increased incidence of 2 to 3 c/sec. spike-wave seizure discharges.

Hydrocortisone produced essentially no change in serum sodium or chloride concentrations but did cause a significant elevation in serum potassium in five of the seven subjects studied. The electroencephalographic changes in these subjects could not be correlated with this electrolyte shift.

Corticotropin induced changes in the electroencephalogram in a patient with a functionally inactive adrenal cortex, suggesting that it may have a direct effect upon cerebral electrical activity.

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Massive Doses of Vitamin B12 in Treatment of Schizophrenia

ALEX D. POKORNY, M.D., Houston, Texas

During the past few years vitamin B_{12} has been used successfully in the treatment of various disorders of the nervous system, especially various painful neuropathies. When solutions of greater potency became available, it was found that doses of 1000γ daily would relieve the pain in many cases of trigeminal neuralgia. The exact mode of action is obscure, but it does not appear to be on a simple replacement basis.[1] An effect on the "deranged intrinsic nerve metabolism" has been suggested.[3] Because of these encouraging reports, it was decided to try massive doses of vitamin B_{12} in treatment of schizophrenic patients, who might also be said to have an obscure disorder of the nervous system. Since the medication appears to have no harmful effects, this was considered to be a sufficient indication for such a clinical trial.*

METHOD

Twenty patients diagnosed as showing schizophrenic reactions were selected for the study. These were subclassified as follows: paranoid, 11; catatonic, 1; hebephrenic, 6; simple, 1; unclassified, 1. The duration of overt psychotic symptoms varied from a few weeks to many years, but the majority of the patients were chronic schizophrenics. An attempt was made to secure a patient group that had not had shock therapy. This was not fully successful, and of the final group, two had previously had insulin shock and four had had E. C. T. These were then assigned randomly to an experimental group of 10 patients and a control group of 10 patients.

It was found later that the experimental group had an average age of 36.9 years, while the control group averaged 30.1 years. (Much of this difference was due to the presence of a 63-year-old man in the first group.) Otherwise, the groups were well matched (for subtype of illness, duration of illness before treatment, previous shock therapy, and, of course, for male sex and war veteran status). The drug was packaged in 5 cc. vials, and identical-appearing placebo vials were made up of dilute phenolphthalein solution. The vials were numbered and were distinguishable by a code known only to the pharmacy and the experimenter, who wrote orders for medication but otherwise had no contact with the patients. In this arrangement, the observations on the patients were made by the ward staff, none of whom knew which were the experimental patients. Furthermore, there was no chance for the patients to be influenced subtly by either being or not being expected to improve by members of the nursing and medical staff. All patients were started on placebo injections for one week. Then the experimental patients were then given 1000γ of vitamin B_{12} I. M. daily, in three divided doses, for a period of 30 days, and the placebo group received a similar volume of injection on the same schedule.

The criteria used for improvement were the over-all clinical impression of the ward psychiatrists, as reflected in the progress notes, and observations of the nursing staff, as recorded in the nursing notes.

RESULTS

Six patients of the 20 improved during the month of injections and in the succeeding few weeks. Three of these were in the vitamin B_{12} group, and three were in the placebo group. Follow-up for periods ranging from 10 to 22 months did not reveal any difference

From the Veterans Administration Hospital, Houston, Texas, and the Department of Psychiatry and Neurology, Baylor University College of Medicine.

* The Vitamin B_{12} for this study was supplied by Merck & Company, Inc.

in the two groups in terms of improvement: Five from each group had been discharged as in remission, with one readmission from each group; two from each group were still hospitalized, and three from each group had been transferred to another hospital or placed on trial visit.

SUMMARY AND CONCLUSIONS

A course of massive doses of vitamin B_{12}, 1000γ daily for 30 days, did not alter the course of schizophrenic illness in 10 patients, as compared with a group of 10 controls, with follow-up periods ranging from 10 to 22 months.

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News and Comment

GENERAL NEWS

Fifth Annual Institute in Psychiatry and Neurology.—The Veterans Administration Hospital, Lyons, N. J.; the New Jersey Neuropsychiatric Association, and the New Jersey District Branch of A. P. A. will hold their Fifth Annual Institute in Psychiatry and Neurology Wednesday, April 13, 1955, at the Veterans Administration Hospital, Lyons, N. J. Moderators: Daniel Blain, M.D.; Stephen P. Jewett, M.D.; Nolan D. C. Lewis, M.D.; Harvey J. Tompkins, M.D.

At the scientific sessions, the following panels are presented:

Forenoon:

Role of the Psychiatric Social Worker in Psychiatric Treatment	Dr. Viola Bernard
Direct Analysis in the Therapy of Psychoses	Dr. John N. Rosen
Shock Therapy *vs.* Psychotherapy in Psychoses	Dr. T. R. Robie

Afternoon:

Relationship of Psychoanalysis to Psychiatry and Neurology	Dr. M. Ralph Kaufman
What Is the American Psychiatric Association?	Dr. R. Finley Gayle Jr.
A Critique of Psychosomatics	Dr. Morris Herman

The after-dinner address, by Dr. Francis J. Braceland, will be Psychiatry in History and Literature.

Registration fee is $1.00, which will include a copy of the proceedings of the Institute. Military personnel and full-time Veterans Administration personnel are exempt. Additional information may be obtained from Crawford N. Baganz, M.D., Manager.

Effects of Chlorpromazine on Metabolism in Central Nervous System

R. G. GRENELL, Ph.D.
J. MENDELSON, B.A.
and
W. D. McELROY, Ph.D., Baltimore

A constantly increasing number of clinical reports has been appearing in the literature concerned with the effectiveness of a new drug in the treatment of certain neuropsychiatric disorders. The drug, in this country, is called chlorpromazine. It has been referred to in France (where the first clinical studies were carried out) as Largactil, or 4560 R. P.[1] (Largactil is also its name in Canada). Chemically, this compound is 3-chloro-10-(γ--dimethylaminopropyl)-2-phenothiazine hydrochloride. It has a number of interesting pharmacological properties, which recently have been described (publications of the Rhône-Poulenc Special Research Laboratories and the Smith, Kline & French Laboratories).

The clinical reports * agree in large measure that chlorpromazine appears to be useful in "the management of anxiety, agitation and manic states in psychoneurotic and in psychotic patients." It has been beneficial in a variety of conditions presenting a picture of psychomotor excitement, and Winkelman [3] has concluded that "it can reduce severe anxiety, diminish phobias and obsessions, reverse or modify a paranoid psychosis, quiet manic or extremely agitated patients, and change the hostile, agitated, senile patient into a quiet, easily managed patient." Lehmann and Hanrahan [2] have discussed the physiological and psychological effects of the drug and pointed out that it appears to have an inhibitory effect on certain functions of the central nervous system. They, as well as many of the other clinical investigators, have considered the problem of the mode of action of this substance. Little is known, however, in regard to this very fundamental question. It was, therefore, the purpose of the present study to attempt to discover whether or not the drug induced any significant change in intracellular metabolism in the central nervous system.

METHOD

The procedures used in these experiments were designed to yield quantitative data relative to three biochemical factors fundamental to the metabolism of central nervous system neurons of the adult male white rat. These factors are as follows:

1. The rate of oxygen uptake
2. The utilization and synthesis of high-energy phosphate bonds
3. The direct acetylation reaction

The rate of oxygen uptake was determined on rat cerebral cortex by the conventional Warburg technique. Adult male white rats weighing from 300-400 gm. were injected intraperitoneally or subcutaneously with 50 and 10 mg/kg. of chlorpromazine, respectively. They were killed by decapitation one-half hour after injection, along with control animals which had received intraperitoneal or subcutaneous injections of isotonic saline solution. No anesthetic was used at any time. The brain was removed rapidly and placed immediately in iced homogenizing solution consisting of the following:

0.04 M $MgCl_2$
0.06 M KCl
0.04 M nicotinamide

The chlorpromazine used was furnished by Smith, Kline & French Laboratories, Inc.

The Psychiatric Institute, University of Maryland Hospital, and Department of Biology, The Johns Hopkins University.

This investigation was partially supported by Contract N7-onr-39706 between the Office of Naval Research and the University of Maryland, and by a grant of the U. S. Public Health Service, M-795(R).

* References 2 through 5, etc.

TABLE 1.—*Effect of Chlorpromazine on Rate of Oxygen Uptake and in Vivo Adenosinetriphosphate Content of Rat Cerebral Cortex*

Group	Average Respiration *	ATP Content †
Controls	195	15.0
Experimental rats. Dose 10 mg/kg.	207	17.0
Controls	206	16.4
Experimental rats. Dose 50 mg/kg.	209	27.9

* Respiration is recorded in terms of cubic millimeters O_2/125 mg. tissue, wet wt/90 min.
† ATP is recorded in terms of micrograms per 125 mg. tissue, wet wt/90 min.

TABLE 2.—*Effect of Chlorpromazine on Sulfanilamide Acetylation by Rat Cerebral Cortex*

	Controls	Chlorpromazine, 50 Mg/Kg.
Sulfanilamide present initially, γ	200	200
α-Sulfanilamide acetylated/90 min., γ	120	120
Average rate of oxygen uptake of system (respiration) *	302	290

* Respiration = cubic millimeters O_2/125 mg. tissue, wet wt. + 0.8 ml. pigeon liver extract/90 min. (The difference seen here is not significant.)

The nicotinamide is necessary to prevent breakdown of Coenzyme I. The pallium was dissected as cleanly as possible away from the remainder of the cerebral hemisphere, quickly weighed, and placed in a pre-iced tube containing three times the tissue wet weight of homogenizing solution. It was then ground for 90 seconds with a steel pestle. Of this 25% homogenate, 0.5 ml. was pipetted into an iced Warburg flask containing, in terms of concentration in the final reaction mixture, 0.02 M sodium pyruvate and 0.05 M phosphate buffer, pH 7.6. The contents of each flask totaled 3 ml., as follows:

Na phosphate buffer	2.12 ml.
Na pyruvate	0.38 ml.
25% homogenate	0.50 ml.

The center well of each flask contained KOH. The flasks were attached to the manometers, placed in the water bath at 37 C, and allowed to equilibrate for 10 minutes. All reactions were carried out in air. Readings were made at 30-minute intervals up to and including 90 minutes.

For the measurements of adenosinetriphosphate (ATP) synthesis, tissue samples were obtained in two ways—in vitro and in vivo. The in vitro specimens consisted of 1 ml. samples of the suspension in the Warburg flasks (as described above), withdrawn after 90 minutes, and pipetted into 3 ml. of boiling H_2O. The tubes were allowed to cool and placed in the deep freeze for future analysis. The in vivo specimens were obtained from animals similarly injected with either chlorpromazine or isotonic saline. Immediately after decapitation of the unanesthetized animal, small portions of the cerebral cortex, cerebellum, midbrain (thalamus-hypothalamus), and medulla were removed and extracted in 3 ml. of boiling H_2O. The solution was allowed to cool and was decanted and frozen. The tissue samples were weighed. The ATP determinations were performed according to the method originated by McElroy and described by Grenell, Mendelson, and McElroy.[6]

It has been demonstrated that sulfanilamide can be acetylated by rat brain homogenates in the presence of acetone-dried pigeon liver. This system has been used in the present series of experiments to determine the action, if any, of chlorpromazine on direct acetylation. In addition, these results serve to indicate any effect of the drug on utilization of high-energy P bonds (ATP). The rat brain homogenates were obtained from animals injected and killed as described above for the Warburg procedure. Sulfanilamide was determined by the method of Bratton and Marshall.

RESULTS

The results of this series of experiments are set forth in Tables 1, 2, and 3. Table 1 presents data concerning measurements of rate of oxygen uptake and ATP content of rat cerebral cortex homogenates in control and experimental animals. The two experimental groups differ only in the dose of

TABLE 3.—*Effect of Chlorpromazine on Brain Adenosinetriphosphate* *
(Summary of 36 Extractions)

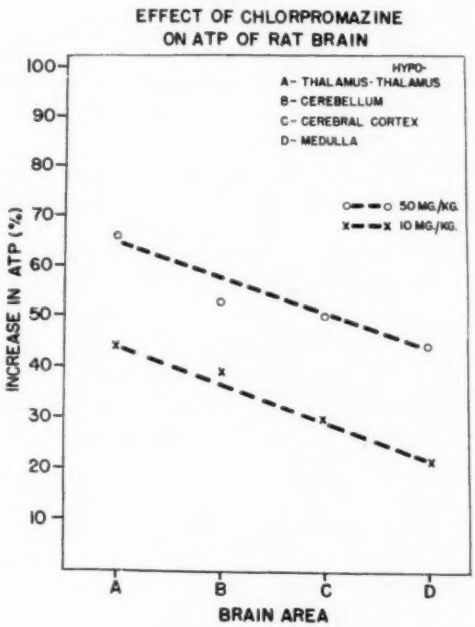
Tissue	Control ATP (Average)	ATP After Chlorpromazine (Average)		Increase in ATP (%) (Average)	
		10 Mg/Kg.	50 Mg/Kg.	10 Mg/Kg.	50 Mg/Kg.
Cerebral cortex	75.15	104.55	150.37	29	50
Thalamus-hypothalamus	62.50	94.20	143.61	44	66
Cerebellum	71.79	118.17	153.80	39	53
Medulla	67.89	85.59	102.30	21	44

* ATP recorded in micrograms per gram of tissue, wet weight.

chlorpromazine; one group was injected with 50 mg/kg. and the other with 10 mg/kg. (the "physiological" dose). It is obvious that no significant change in cortical respiration takes place with either of these doses of the drug. This does not mean that no metabolic change has occurred or that there is no change in functional status of the cells. In fact, that a marked alteration in metabolism has taken place is shown by the increase in ATP.

Since the so-called "resting" respiration was not affected, it was essential to examine some of the reactions and pathways chemically related to the activity of the neurons and to the transmission of impulses. The first mechanisms investigated and reported here are those concerned with the utilization and synthesis of adenosinetriphosphate (ATP). The utilization of ATP was tested by measuring the in vitro rate of acetylation reaction to be carried through to completion at the normal rate, ATP must be utilized at the normal rate. The reaction is identical with the one which, in vivo, is essential for the synthesis of acetylcholine. The system used here allows both high purity of assay and high degree of quantitation of its elements. Table 2 presents the acetylation data along with measurements of rate of oxygen uptake. The latter were taken to show that the cortical tissue was in a normal respiratory state; the values are higher than those in Table 1 because of the presence of pigeon liver (in addition to the cortical tissue) in the acetylation system. No change in the rate of acetylation of sulfanilamide is seen, even with the high dose of chlorpromazine of 50 mg/kg.

The most interesting positive results were obtained on direct measurement of ATP content (steady-state level) of cerebral cortex, cerebellum, midbrain, and medulla of control and chlorpromazine-injected rats. These data have been summarized in Table 3. It can be seen from the Table and from the Figure that an increase in ATP is found in all the central nervous system areas analyzed, consequent to injection of both 50 mg/kg. and 10 mg/kg. (the physiological dose). (This is also true for the in vitro ATP analyses of extracts of preparations run in the Warburg apparatus for 90 minutes. In this case, the ATP increases following injection of both 10 mg/kg. and 50 mg/kg. of the drug were, respectively, 12% and 41%.) It is further apparent that two important points arise out of these data: (*a*) The thalamic-hypothalamic area normally contains the lowest ATP concentration of all four regions analyzed, and (*b*) after chlorpromazine injection the increase in ATP



is not the same in all areas but is greatest in the thalamic-hypothalamic region, followed, in order, by cerebellum, cerebral cortex, and medulla. The cortex, which normally shows the highest concentration of ATP and is so frequently the most susceptible brain area to stresses of all kinds, does not react to chlorpromazine with the expected sensitivity (at least with regard to change in ATP concentration). The major points observed, then, are that (1) ATP utilization appears to be interfered with, and (2) the effect is selective. The most marked

increase in ATP is seen in the thalamic-hypothalamic area (of the four areas examined).

COMMENT

A number of interesting statements have appeared in the literature concerning generalized effects of chlorpromazine on behavior, and some attempt has been made to relate these effects to certain physiological phenomena. The changes in behavior pattern would seem largely to reflect effects on centers related to so-called "primitive" subcortical activity. It has been reported[2]: "The sedative effect of chlorpromazine is not associated with clouding of consciousness, impairment of judgment or disinhibition of affect." These observations on patients treated with the drug suggested to the majority of clinical investigators that "cortical metabolism is little affected by chlorpromazine and that the possible site of its action is located in the activating reticular substance." The hypothalamus also suggested itself as an affected locus. This indication of hypothalamic sensitivity to the drug has not been inferred from the ganglioplegic effects alone. In addition, the drug would appear to affect, primarily, subcortical structures "that are concerned with maintaining psychomotor drive and wakefulness."

Despite all these astute clinical observations and interesting indications, the physiochemical mechanism involved has not been clarified. The studies reported in the present paper comprise an initial effort to answer two major questions:

1. What factors are related to or involved in the action of chlorpromazine?

2. Can any metabolic shifts be demonstrated which are associated with the observed change in behavior that the drug induces?

Part of the decision regarding the experimental approach to these problems was based on the gross behavioral changes observed in the animals shortly after injection of the drug. Within a quarter of an hour after injection the rats were lethargic and remained relatively motionless in any position in which they were placed. None of the usual activity of the normal rat—sniffing, running about, etc.—was in evidence. It appeared that the usual stimuli from the external environment (and perhaps the internal as well) were no longer evoking the usual responses. Even placing these animals in an emergency situation (in this case dropping them into a sink full of water) failed to produce the appropriate response for survival. Despite this altered primitive behavior picture, the reflexes appeared intact—both the corneal reflex and the leg withdrawal consequent to pinching the toe seemed normal. In general, then, the characteristics of this hypoactive state suggested an "indifference" to messages coming into the central nervous system. Certain neurophysiologic concepts possibly related to this state will be discussed in a later paper.

These and other considerations led to the conclusion that it might be of value to investigate some of the intracellular energy factors in various cell groups of the central nervous system, i. e., oxidative mechanisms and high-energy phosphate bonds. The results obtained indicate that oxidative, respiratory mechanisms are not being interfered with. Adenosinetriphostrate, however, is piling up. It is not being utilized at the normal rate. These results bring up several basic questions. Since ATP is being utilized at the normal rate in the direct acetylation reaction, how and where is its use being interfered with? The answer to this question remains to be determined. The relationship between ATP and activity suggests, however, that with the obvious reduction in activity the need for ATP sharply declines. This decline allows it to pile up. We do not know, moreover, that another possibility does not exist; namely, that activity is reduced because of an inability to breakdown ATP.

This question also entails consideration of the status of acetylcholine in the chlorpromazine reaction. If acetylcholine formation is significantly reduced, it is not the result of interference with direct acetylation. Nonetheless, two possibilities suggest themselves: Either there is a reduction in free acetyl-

choline, or there is some degree of suppression of the conversion of bound acetylcholine to the free form. It is hoped that future measurements will help to answer this phase of the problem.

Another interesting question is raised by the selectivity of the ATP effects of the drug. The fact that the greatest increase in ATP is seen in the tissue of the hypothalamic area would substantiate the clinical impression resulting from observation of Thorazine-injected patients. At first, however, it would seem rather difficult to attempt to explain how the cerebellum (the second most severely affected area of the four examined) fits into the behavior picture. Although this answer has yet to be definitely established, a tentative hypothesis can be based on neurophysiological studies, such as that of Zanchetti and Zoccolini.[7] These investigators observed somatic and autonomic outbursts of sham rage in thalamic cats during and immediately after cerebellar stimulation. The responses were abolished by destruction of cerebellar structures or by rostral midbrain electrocoagulation. It is inferred from these results that what appears to be direct cerebellar activation of hypothalamic centers could be mediated through the fastigioreticular tract and ascending reticular formation of the brain stem.

The observations reported here serve only as a clue, and not as a final answer, to the mechanism of action of the drug. Even more important, however, is the fact that they provide definite evidence for the association of a marked intracellular metabolic shift with a marked shift in behavior pattern.

SUMMARY AND CONCLUSIONS

Measurements have been made on albino rat brain of rate of oxygen uptake, rate of direct acetylation of sulfanilamide, and of adenosinetriphosphate (ATP) levels before and after administration of chlorpromazine.

The drug does not appear to affect either cortical respiration or the in vitro rate of acetylation. It does, however, induce a marked increase in ATP levels, i. e., a decrease in utilization of ATP. This ATP effect is selective. The greatest increase was found in a midbrain area, followed, in that order, by cerebellum, cerebral cortex, and medulla. These findings are discussed in relation to the changes in activity and general behavior pattern consequent to injection of chlorpromazine.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Benjamin Boshes, M.D., *President*

Oscar Sugar, M.D., *Secretary*

Regular Meeting, Oct. 12, 1954

Glioblastoma of the Frontal Lobe with Five-Year Survival. Dr. Harold C. Voris.

A 31-year-old white woman was hospitalized Dec. 19, 1948, because of headache awakening her from sleep for two and one-half months, morning nausea and vomiting for three weeks, and occasional double vision. Examination revealed bilateral papilledema, moderate weakness of the left lateral rectus, and an equivocal Babinski sign on the right. After ventriculography, a bilateral frontal craniotomy was performed. A soft, friable neoplasm occupying most of the left frontal lobe anterior to the coronal suture was grossly completely removed. Histologic diagnosis was glioblastoma. High-voltage roentgen radiation was given in January, 1949. Because of recurrent drainage, the bone flap was removed in March, and on July 5, 1949, tantalum cranioplasty was carried out. A small tissue nodule was curetted from the dura mater at this time and later diagnosed as actively growing glioblastoma. The patient and her husband decided against further roentgen therapy. Slight difficulty with wound healing led to plastic procedures in August and September, 1949, but since that time the patient has been in excellent health. When examined just prior to presentation here, no papilledema was evident.

DISCUSSION

Dr. Percival Bailey: I looked at the sections. A tumor of the frontal lobe in an adult which has a large number of abnormal mitoses is usually a glioblastoma. The sections, as I recall them, did not appear to be typical of that sort of tumor. If I remember these sections correctly, no mitotic figures were seen. I am not sure that this tumor was a glioblastoma. Most of the cells were spindle-shaped. Rarely could anyone say that a glioblastoma had been extirpated so completely that it never recurred. Dr. Sachs and I have quarreled for many years about that, he maintaining that an attempt should always be made to remove them, and I maintaining that rarely has anyone ever succeeded in doing it. I did so once, but I am not proud of it and would just as soon forget it. The man has lived since 1939 as a charge on society, on relief all those years. I am not sure that is so remarkable an achievement.

Dr. Paul Bucy: This single case of Dr. Voris again illustrates the value of attempting as complete an extirpation of a glioma as is possible, even though it looks as though there is little chance of success. Although one often hears the opinion expressed that all cerebral gliomas are ultimately hopeless, this is not true. In many instances useful life can be maintained for many years, and in some the tumor can be removed and the patient cured. Approximately 20 years ago I completely extirpated gliomas from the occipital lobes of two young women. Both patients are still alive, active, and well.

I have some reservations as to the type of glioma in Dr. Voris' case. It would not be possible to classify it from the lantern slides.

Nonsyphilitic Interstitial Keratitis Associated with Deafness—Cogan's Syndrome: Report of a Case. Dr. Hüsameddin K. Gökay.

A typical case of Cogan's syndrome in a 18-year-old woman was presented. This syndrome, which was first described by Cogan in 1945, is characterized by sudden onset of ocular or vestibuloauditory symptoms. The ocular symptoms consist of photophobia, blurring of vision, and ocular pain, followed by interstitial keratitis. The vestibular symptoms begin with tinnitus, severe vertigo, nausea and vomiting, and bilateral progressive loss of hearing. The ocular symptoms may or may not precede the vestibular ones. The corneal opacities disappear in the course of a few months, as is illustrated in the reported case. The deafness usually lasts longer, and it is permanent in some cases. The hearing improved in 25% of the 19 cases reported since

1945. The etiology of the condition is unknown; the therapy is empirical. The syndrome should be differentiated from syphilitic interstitial keratitis and Ménière's disease, and also from such conditions as the Vogt-Koyanagi syndrome, Harada's disease, and Heerfordt's disease, or uveoparotid fever.

DISCUSSION

DR. IRVING C. SHERMAN: Dr. Gökay should be thanked for bringing to our attention a condition which we as neurologists do not often see. I had contact with the first case he mentioned, which was reported from Michael Reese Hospital. As Dr. Gökay described the case, the diagnosis sounded very simple, but actually, as a diagnostic problem for me, as the neurologist, the case became very involved. At first, this patient did not have any eye involvement. The sudden appearance of vertigo, nausea, vomiting, and bilateral rapidly progressive deafness in a previously healthy young girl presented a perplexing problem. At first, the otologists treated the condition as a Ménière syndrome. Another neurologist and I felt for a while that the case was one of some type of brain stem disease, although we made this diagnosis without any strong conviction. During the period of observation some of our psychiatrically minded residents felt there were strong reasons to believe the case might have a hysterical basis. Indeed, one of them felt he was accomplishing something briefly with the use of psychotherapy (which had to be carried on in shouting) while the patient was under intravenous sodium amobarbital. However, the picture became clear when the keratitis developed, and one of our industrious internists combed the literature and found Cogan's description.

I think the follow-up history in this case may be of interest. The patient was severely ill for eight months. Polyarteritis, with gastrointestinal and cardiac involvement, developed. For a time, it looked as though she could not survive.

She has now recovered, with the residue of complete deafness. However, attesting to her lack of psychiatric disturbance is the fact that she is happily married and has several children.

DR. PERCIVAL BAILEY: This woman happened to be my patient. I did not know what the difficulty was; so I took her over to Illinois Neuropsychiatric Institute; I do not remember who finally made the diagnosis. She has less defective hearing than most patients with the disease.

Ophthalmoplegic Migraine. DR. ADRIEN VERBRUGGHEN.

This paper, entitled ophthalmoplegic migraine, might better be called "the pathogenesis of ophthalmoplegic migraine." It concerned a discussion of some of the problems involved in explaining the oculomotor paralysis in this condition. The current theory of spasm and dilatation of cerebral blood vessels was correlated with the recently demonstrated anatomical relationships between the oculomotor nerves and various parts of the internal carotid and vertebral systems. These facts were supported by lantern slides demonstrating the relationships. The study of this matter was stimulated by a case of ophthalmoplegic migraine in a girl of 12 years who was first seen with this condition when she was 14 months old. The case was thoroughly studied and was reported in this paper.

DISCUSSION

DR. MEYER BROWN: I should like to ask Dr. Verbrugghen whether this patient had attacks of headache without ophthalmoplegia, and whether or not the fundus was examined for vasomotor changes during an attack.

DR. ADRIEN VERBRUGGHEN: The question was asked regarding ball-valve tumor. I have never seen a ball-valve tumor in a patient who had ophthalmoplegia.

The ophthalmoplegic migraine under discussion differs from the ophthalmic variety with homonymous hemianopsia. I looked back in the ARCHIVES and read of a case of ophthalmoplegic migraine which Foster Kennedy presented at a meeting of the New York Neurological Society. The discussion was interesting. When I showed my patient at the Neuropsychiatric Institute here, there was considerable debate, and there were not many who had seen a case of ophthalmoplegic migraine. That is why I thought the case worth presenting. It was authentic because of the arteriograms, and also because the patient had been followed since she was 14 months old. We never saw the vasodilatation and the vasospasm, or the nausea and vomiting, because these symptoms always came first, before the full-blown ophthalmoplegia. She did not have the ophthalmoplegia at the same time as the headache and the nausea and vomiting, but woke with it the following morning.

Defective Temperature Regulation in Patients with Cervical Spinal Cord Lesions.

DR. ALEX J. ARIEFF and DR. RICHARD CROUCH, Hines, Ill.

Patients with chronic physiologically complete cervical cord lesions, with the higher centers cut off, when immersed in cold water at 65 F. lose 1.4 to 1.9 degrees (F), as compared with the controls, who lost only 0.5 to 0.7 degrees (F). The return to normal after being out of cold water is slower in the paraplegic patients.

The stimulus to heat production when patients are immersed in cold water is almost one-third of normal, as measured by oxygen intake.

Patients with chronic physiologically complete cord lesions immersed in hot water at 102 F for 45 minutes gain a mean of 3.6 degrees (F), as compared with a mean gain of 1.9 degrees (F) in normal (control) patients. The patients show, also, a slower return to normal.

Patients in a hot-air environment of 65 to 100 F show a range of 96 to 100 F, as compared with other patients with lower spinal cord lesions in a similar environment, whose range was 98 to 98.6 F. In patients with physiologically complete lesions there were almost four times as many subjective complaints as in other patients in a similar environment.

Although normal man is not entirely homeothermic at extreme temperature environments, chronic spinal man has much more marked defective temperature control because of the cutting off of the hypothalamic centers.

All these observations show processes of centrally acting stimuli for heat regulation.

DISCUSSION

DR. NORMAN B. DOBIN: Since Dr. Arieff and Dr. Crouch cite extensively the work on the influence of environment on the body temperature in normal man, published by my co-workers and myself, I should like to add two pertinent comments. They state that in normal subjects, studied by immersion in cold water, the body temperature was not taken after completion of the experiments. This is true. However, the students serving as experimental subjects were closely observed and reported to me that invariably they felt so cold and shivered so much that they were obliged to wear their topcoats in the classrooms until 3 p. m. because of inability to stay warm. The experiments were done at 8:00 a. m. and completed by 9:00 a. m. in the months of October and November.

My second comment deals with the reasons for the elevation of body temperature in the hot, and a fall in the cold, immersion experiments. It is not related at all to the elevation in "calories," as cited by Drs. Arieff and Crouch, since these were elevated in both the hot and the cold immersion experiments, but is related, rather, to the factor of heat storage. Ordinarily, a person maintains a normal body temperature because body heat production is equal to heat loss. Thus, there is no heat storage. When a subject is in such surroundings as those in hot-water immersion experiments, where heat cannot be dissipated, heat storage becomes a very positive quantity, as charted on a graph, and body temperature goes up. In cold immersion experiments, heat loss is somewhat greater than heat production, but what is even more striking is that the resulting calculated heat storage becomes a very negative quantity, as we have shown graphically, and the body temperature drops. The change in heat storage in either of the experiments was directly proportional to the volume and surface area of the body immersed in the water.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CARBOHYDRATE METABOLISM IN BRAIN DISEASE. D. H. HENNEMAN, M. D. ALTSCHULE, and R. M. GONCZ, A. M. A. Arch. Int. Med. **94**:402 (Sept.) 1954.

Henneman and her associates made studies of carbohydrate metabolism in the fasting state and after administration of glucose in patients with schizophrenic, manic-depressive, and involutional psychoses. All the patients had no other intercurrent disease, were well nourished and not debilitated, were not receiving shock therapy, and were cooperative during the study; the women had normal menstrual function. All subjects had a high carbohydrate intake, in addition to their adequate normal diets, for three to five days before each experiment. They were at rest throughout the study and in the fasting state at the time the initial blood specimen was taken. The fasting blood concentrations of pyruvic, citric, and α-ketoglutaric acids and of inorganic phosphate were normal; one-third of the patients showed significant elevations of true blood glucose and lactic acid concentrations.

Changes observed in the patients after the ingestion of 100 gm. of glucose overlapped those found in the normal subjects, but there were significant differences in the changes in all blood constituents measured: In the psychotic patients there was a lag in the return to the fasting level of the true blood glucose, an excessive elevation in lactic and pyruvic acids, a rise, rather than a fall, in citric and α-ketoglutaric acids, and an increased and prolonged fall in serum inorganic phosphate. Clinical status could be correlated with biochemical abnormality; patients with psychosis of recent onset manifested at least three, and frequently all, of the abnormalities, whereas those with chronic psychosis failed to exhibit the abnormal changes in blood lactic acid and inorganic phosphate but usually showed the citric and α-ketoglutaric acid changes to an exaggerated degree.

In an attempt to correlate the clinical status of the acute patient with the chemical abnormalities, tests were performed before and after treatment whenever possible. The first study was made within the first week after admission to the hospital, and the second test was made at least two weeks after the last insulin or electric shock treatment. It was found that remission following treatment was correlated with biochemical changes toward the normal values.

The intravenous infusion of 50 gm. of dextrose in a two-hour period in normal and psychotic subjects showed differences similar to those seen after the ingestion of 100 gm. of glucose. However, when the 50 gm. of dextrose were infused rapidly in a one-half hour period, the normal and psychotic subjects showed comparable changes. The reason for this effect of the rate of infusion of dextrose is unknown; although the half-hour infusion of dextrose was comparable to the ingestion of 100 gm. of glucose in normal subjects if only changes in blood glucose concentration were measured, the two tests were found not to be comparable if changes in breakdown products of glucose were measured.

The authors discuss the relation of the biochemical abnormalities observed after glucose administration in patients with psychosis to those observed in starvation, to those found in other organic brain diseases, and to abnormal ketosis. Data presented here indicate that patients with the psychoses studied show measurable biochemical abnormalities remarkably similar to those observed in patients with organic brain disease.

ALPERS, Philadelphia.

CEREBRAL INTRAVASCULAR PRESSURE IN CHEMICALLY INDUCED HYPOTENSION. B. WOODHALL, G. L. ODOM, C. R. STEPHEN, C. MCCLURE, and W. R. NEILL, A. M. A. Arch. Surg. **69**:496 (Oct.) 1954.

In a series of 26 neurosurgical patients the blood pressure obtained by the conventional arm cuff method was compared with that obtained by intravascular recording from the radial and cortical arteries (exposed by craniotomy). The basal pressures were compared with the values observed after induction of hypotensive anesthesia with N,N,N′,N′-3-pentamethyl-N-N′-diethyl-

3-azopentane-1,5-diammonium dibromide (Pendiomid), hexamethonium chloride, and camphor sulfonate trimethaphen (Arfonad). For the intravascular recording a Sanborn electromanometer was used.

Normally the pressure obtained by direct recording from the radial artery is lower than that obtained by the cuff method. The pressure in cortical arteries is still lower, depending on the caliber of the vessel.

When in the course of hypotensive anesthesia the intravascular pressure in the radial artery falls below 50 mm., the pressure in the arm cuff may not be recordable at all; in other words, the arm cuff method becomes unreliable when the blood pressure reaches a critical level which may result in anoxic tissue damage. Under hypotensive conditions the author found that the values for intravascular pressure of the radial and cortical arteries showed good correspondence.

LIST, Grand Rapids, Mich.

UTILIZATION OF BRANCHED CHAIN ACIDS IN CHOLESTEROL SYNTHESIS. K. BLOCH, I. C. CLARK, and I. HARARY, J. Biol. Chem. **211**:687, 1954.

The branched chain acids 3-C^{14}-beta-hydroxy-beta-methylglutaric acid, 3-C^{14}-cis-beta-methylglutaconic acid, 3-C^{14}-beta-hydroxyisovaleric acid, and 3-C^{14}-beta-dimethylacrylic acid when fed to rats are converted to cholesterol without prior breakdown to acetate or acetoacetate. The acids are converted to cholesterol or to a small degree in liver homogenates.

PAGE, Cleveland.

A STUDY OF METAL IONS IN THE CENTRAL NERVOUS SYSTEM: I. PRELIMINARY CONSIDERATIONS. W. H. HARRIS, J. A. BEAUCHEMIN, H. M. HERSHENSON, S. H. ROBERTS, and G. MATSUYAMA, J. Neuropath. & Exper. Neurol. **13**:427 (July) 1954.

The authors report their preliminary observations on the qualitative distribution pattern of certain metal ions in various areas of the brain. The brain was divided into portions comprising the anatomic lobes, the insula, the basal ganglia, the brain stem, and the cerebellum, and each portion was digested by a standard method and the resulting solution analyzed spectrographically (range, 2400 to 3600 A.). Some 14 metal ions were found consistently. The majority of the metals found were present in all areas examined, although a considerable variation in concentration was found from area to area.

SIEKERT, Rochester, Minn.

EXPERIMENTALLY PRODUCED RED SOFTENING OF THE BRAIN. C. FAZIO and U. SACCHI, J. Neuropath. & Exper. Neurol. **13**:476 (July) 1954.

Fazio and Sacchi believe that a transitory or incomplete interruption of blood flow (as with a transitory air embolus) plays a fundamental pathogenic role in the genesis of red softening. With injection of air into the common carotid, foci of red softening are frequently produced. Red softening appears more commonly and more extensively if cerebral venous stasis is produced at the same time. The red softenings do not occur if epinephrine is injected immediately after the introduction of air, but the red softening is produced if an interval of approximately 30 minutes is allowed to occur between the air and the epinephrine injections. The necessity of this interval between embolus and hypertensive crisis suggests that by means of the emboli, particular conditions are established which facilitate the extravasation of blood from the vessels. This alteration probably introduces functional and anatomical alterations of the vessel walls and of the perivascular tissues. An arrest or a remarkable slowing up of the circulation determines local production of metabolites, which have a vasodilatory effect. Extensive and large emboli produced by the introduction of kaolin in the carotid arteries, followed by arterial hypertension and cerebral venous stasis, did not produce cerebral red softening, suggesting that collateral circulation is also important.

SIEKERT, Rochester, Minn.

STIMULATION OF THE AMYGDALOID NUCLEAR COMPLEX IN UNANESTHETIZED CATS. B. KAADA, P. ANDERSEN, and J. JANSEN, Neurology **4**:48 (Jan.) 1954.

The main purpose of the experiments here reported was to correlate the various somatomotor and autonomic effects which can be elicited by stimulation of the amygdala in cats with the different nuclei of this complex. Second, a more detailed study of the somatomotor and auto-

nomic effects was made possible by stimulating the unanesthetized, freely moving animal through implanted electrodes and by cinematographic analysis of the responses. Further, it was of particular interest to determine whether any emotional type of reactions could be produced by stimulation, and also whether seizures resembling epileptic automatisms in humans could be precipitated from the amygdala, because such responses had been observed on electrical stimulation of the periamygdaloid cortex in cats and humans.

These workers found that electrical stimulation of the amygdaloid nuclear complex in unanesthetized cats elicited complex somatomotor and visceromotor effects: contraversive movements, tonic and clonic movements of the extremities, licking, sniffing, chewing, and inhibition of respiratory and other spontaneous somatomotor activities; pupillodilation, salivation, micturition, defecation, and piloerection. These responses were obtained mainly from the phylogenetically old anteromedial division of the amygdaloid nuclei, which receives fibers from the olfactory bulb and which projects to the septal, preoptic, and hypothalamic areas.

Stimulation of the phylogenetically younger basolateral division, which appears to have no direct connection with fibers from the olfactory bulb and whose efferent projections are unknown, produced behavior changes very similar to those obtained by stimulating the hippocampus and the medial prefrontal, limbic, retrosplenial, and hippocampal gyral cortices, indicating functional relationships among all these structures. This response consisted of searching movements to the contralateral side associated with bewilderment and anxiety, and sometimes with fear, anger, and fury.

The authors discuss their results in relation to temporal lobe seizures. They believe that the amygdala plays an important role in certain types of epileptic automatisms.

ALPERS, Philadelphia.

METRAZOL ACTIVATION AS A DIAGNOSTIC ADJUNCT IN ELECTROENCEPHALOGRAPHY. F. J. MOORE, P. KELLAWAY, and N. KAGAWA, Neurology **4**:325 (May) 1954.

It is generally accepted that approximately 10% to 25% of epileptics have "normal" routine interseizure electroencephalograms. Even among the 75% to 90% with abnormal records, a considerable number of the abnormalities are nonspecific in character and may be found in a significant portion of controls. A specific activation technique is necessary in order to increase the diagnostic efficiency of electroencephalography.

Moore and his associates made pentylenetetrazol (Metrazol) activation studies in 250 subjects, using the slow technique. Of these, 120 were a highly selected group, meeting strict criteria of normality. Eighty-one patients presented diagnostic problems with equivocal epileptoid symptoms and/or abnormal electroencephalograms, and 49 were definite convulsive cases having nondiagnostic electrographic findings.

Fifty-four per cent of normal controls under the age of 30 gave a positive response, and 62% of these were the spike and wave type. Of 61 normals over the age of 30 years, 16.4% showed a positive response. Thus, age seems to be an extremely important factor in determining the electrographic response to Metrazol. Sex and weight are factors whose influence on the reactivity to Metrazol needs further study.

None of the normal group showed focal abnormalities with Metrazol. The slow technique, was, however, very effective in activating focal abnormalities in the abnormal group.

In bringing their discussion of Metrazol activation down to one important question: "Can the test be used for the diagnosis of epilepsy?" the authors feel that their results suggest that this answer must be both "Yes" and "No." It seems to be diagnostically valid when it gives a focal response, as no such responses were produced in their normal group. On the other hand, a generalized paroxysmal response, even when it is a spike and wave pattern, cannot be considered reliable evidence of a convulsive disorder.

ALPERS, Philadelphia.

LOCALIZATION OF BRAIN LESIONS BY MEANS OF RISA. J. G. RUSHTON, H. J. SVIEN, and E. J. BALDES, Proc. Staff Meet., Mayo Clin. **29**:478 (Aug. 25) 1954.

A total of 121 patients were studied with RISA (radioactive iodine in human serum albumin). Of this group, 37 were "controls," and the remaining 84 had intracranial lesions.

Of those patients with non-neoplastic lesions, 22 were victims of "strokes." Of these, nine patients had lesions caused by damage occurring six or more weeks before the test, and in none of these patients was a localization obtained. Of the remaining 13, with more "recent" damage,

localization was encountered in 4 patients. Ten patients had degenerative lesions of the brain; in none of these was a localization found. Six patients with subarachnoid hemorrhage were found to have aneurysm of the circle of Willis. In none of these was a localization encountered.

Forty-one patients having verified brain tumors were studied with RISA. Of 6 meningiomas, 3 were localized; of 18 astrocytomas, 5 were localized; of 12 miscellaneous neoplasms, 3 were localized.

There were six metastatic brain tumors, two of which were localized. Three cases of subdural hematoma were studied. In two cases positive localization over some part of the hematoma was present. In one case a clinical diagnosis of acute brain abscess in the temporal region was made. Radioactive isotope studies gave a positive localization in the temporal region.

The results of this study, according to Rushton and his colleagues, indicate that this procedure is not, in its present stage of development, a useful method for localization of intracranial lesions.

ALPERS, Philadelphia.

Neuropathology

MUCUS-SECRETING CELLS IN COLLOID CYSTS OF THE THIRD VENTRICLE. W. H. MOSBERG JR. and W. BLACKWOOD, J. Neuropath. & Exper. Neurol. **13**:417 (July) 1954.

Mosberg and Blackwood review certain arguments that have been advanced against the theory that the colloid cyst tumors of the third ventricle are derived from a persistent paraphysis. They note that certain embryologists have considered it a very transitory structure in the human embryo and that colloid cysts are consistently found intraventricularly, while the paraphysis is an extraventricular structure. Other authors have considered this tumor to be derived from the choroid plexus of the third ventricle, the reasons being that the capsule is composed of connective tissue and lined by cuboid cells similar to those covering the plexus, and that the only point of attachment of the tumor seems to be the choroid plexus of the third ventricle. The fact that goblet cells have been found in the lining epithelium on one instance was taken as further evidence against a paraphysial origin of the colloid cyst.

The present authors had tissue available for mucicarmine staining in seven cases. A mucinous secretion was present in six cases. Histologic observations on these cases are presented. In addition, the pathologic aspects of 105 cases of colloid cysts from the literature are reviewed.

The relevance of this finding of mucin in the cuboidal or columnar cells lining the cyst and in the cyst contents, according to the authors, is not clear. They feel that the key which will relate the presence of this mucus appears to be as yet undiscovered.

SIEKERT, Rochester, Minn.

METASTATIC AND PRIMARY INTRACRANIAL TUMORS OF THE ADULT MALE. K. M. EARLE, J. Neuropath. & Exper. Neurol. **13**:448 (July) 1954.

In this series of 3901 consecutive autopsies on males, it was noted that metastatic brain tumors were commoner than primary intracranial tumors in the adult male. Of the series, 1498 (37.9%) had a malignant neoplasm somewhere. Ninety-nine had a primary intracranial tumor, and 167 had metastatic tumor of the brain. Thus, 6.6% of all malignant neoplasms in this series were primary intracranial tumors. Eleven per cent of all extracranial malignant neoplasms showed metastases to the brain. Almost all types of primary brain tumors were included, but the glioblastoma multiforme was the commonest primary intracranial neoplasm. The commonest source of metastatic brain tumors was bronchogenic carcinoma. Other primary sources were represented by malignant melanoma, of the large intestine, kidney, and testis, in decreasing order of frequency. Metastatic brain lesions were found to be more frequently multiple than solitary.

SIEKERT, Rochester, Minn.

Meninges and Blood Vessels

RECURRENT TUBERCULOUS MENINGITIS. A. L. HOYNE, J. H. DIAMOND, and A. SCHULTZ, J. A. M. A. **155**:1234 (July 31) 1954.

The authors describe a case of tuberculous meningitis first appearing at the age of 15 in a Negro girl. She was treated with streptomycin intramuscularly for 90 days and was discharged after 119 days of hospitalization afebrile and asymptomatic. The patient was readmitted to

hospital six weeks later with recurring complaints of headache, stiff neck, and vomiting. Another 90 days of streptomycin therapy intramuscularly was started. An audiogram taken after two months' therapy with streptomycin disclosed a moderate hearing loss in the high range above the normal voice. Clinically the patient exhibited no difficulties in hearing. After the course of streptomycin was finished, the patient appeared clinically well and was discharged for follow-up studies.

Seven weeks later she was admitted for the third time because of headache, sleepiness, and inability to move the left arm. Studies over the next two weeks indicated a recurrence of the tuberculous meningitis, and another course of streptomycin was started intramuscularly. After 100 days of streptomycin treatment she was well clinically and was discharged.

The patient remained well, and at the end of six months a lumbar puncture disclosed fluid that was normal in all respects. At the time of the report it was nearly seven years since she first entered the hospital. She has continued to be in good health and has married and had three robust, healthy children, none of whom show any clinical evidence of tuberculous infection and all of whom have negative Mendel (Mantoux) tests.

The authors point out that this case is one of the most prolonged instances of therapy with complete recovery from tuberculous meningitis since the introduction of streptomycin. It shows that tuberculous meningitis can be cured without resort to intrathecal medication. It demonstrates that recurrences do not necessarily mean that recovery is hopeless—they mean only that treatment should again be instituted most vigorously. Finally, the fact that this patient has subsequently undergone three successive pregnancies with no breakdown of either the pulmonary or the central nervous system lesions strongly suggests that healed tuberculous meningitis need not be a contraindication to pregnancy.

ALPERS, Philadelphia.

SPONTANEOUS OCCLUSION OF THE INTERNAL CAROTID ARTERY. E. H. FEIRING, Neurology **4**:405 (June) 1954.

Feiring presents seven cases of spontaneous occlusion of the internal carotid artery encountered among approximately 500 cases studied by angiography for suspected brain tumor or vascular anomaly. All seven patients were males; the mean age was 55 years. The shortest duration of symptoms was two months, and the longest five years. A progressive course characterized the clinical symptomatology in four cases. In the other three cases episodic manifestations occurred frequently of transient duration. The clinical manifestations are discussed. Evidence of associated peripheral or cardiovascular disease was demonstrable in four patients: Two had hypertension and two diabetes.

A normal electroencephalogram was observed in only one case. A slight alternating asymmetry of alpha frequency and a small amount of low- to moderate-voltage sporadic delta activity over both temporal regions were recorded in another case. In the remaining five patients there was slowing of the alpha activity, with some amplitude asymmetry, either higher or lower, and fairly diffuse delta activity, usually with focal accentuations at the frontal and temporal lobes, all on the affected side.

Occlusion of the artery occurred in the neck beyond the bifurcation of the common carotid in five cases. In the remaining two the lesion affected the intracranial component of the vessel. Anatomic verification of the lesion was not obtained in any patient in this series. Feiring indicates the importance of roentgenographic criteria for diagnosis. The arteriograms in these cases are definitive. All patients were subjected to pneumoencephalography. In six cases symmetrically dilated ventricles and/or widened subarachnoid spaces were demonstrated. The seventh case was entirely normal.

Definitive therapy was attempted in only two patients, both of whom were given bishydroxycoumarin U. S. P. (Dicumarol). It was discontinued in one patient soon after treatment was begun because of the occurrence of hemorrhagic phenomena; this patient has since died of a coronary occlusion. The second patient's treatment was discontinued after about a year, when his blood rose considerably. He has improved appreciably and resumed his occupation. Of the remaining five untreated cases, one is psychotic and confined to a mental institution, one is a chronic invalid, another remains unimproved, though not severely handicapped, one died presumably of progressive cerebral vascular disease, and one has improved sufficiently to return to work.

ALPERS, Philadelphia.

Diseases of the Brain

ASSOCIATION OF MATERNAL AND FETAL FACTORS WITH THE DEVELOPMENT OF EPILEPSY. A. M. LILIENFELD and B. PASAMANICK, J. A. M. A. **155**:719 (June 19) 1954.

The prenatal and paranatal records of 564 epileptic children born in Baltimore between 1935 and 1952 showed significantly more complications of pregnancy and delivery, prematurity, and abnormal neonatal conditions than a similar number of matched controls. These abnormalities were just as frequent among epileptic children whose parents did or did not have epilepsy. These epidemiological findings throw some light on the etiology of epilepsy and raise doubts as to the genetic basis of convulsive disorders.

The pattern of factors such as complications of pregnancy, prematurity, and neonatal abnormalities that appear to be associated with epilepsy is similar to that previously found to be associated with cerebral palsy, stillbirths, and neonatal deaths. In a previous paper by Lilienfeld and associates, it was postulated that there exists a continuum of reproduction casualty composed of a lethal component consisting of stillbirths and neonatal deaths, and a sublethal component consisting of cerebral palsy. The results of the present study suggest that this sublethal component should also include epilepsy. This observation, together with the fact that approximately one-third of persons with cerebral palsy have convulsive seizures, suggests that cerebral palsy may be a result of a severer type of brain damage than is epilepsy. The results are sufficiently suggestive to warrant the continuance of similar studies concerning other possible components of this continuum. They also warrant giving serious consideration to the possibilities of establishing concurrent studies in which a group of infants classified by these maternal and fetal factors could be followed, so that one can actually measure the risks of various neurological conditions associated with these maternal and fetal factors developing.

ALPERS, Philadelphia.

VENEZUELAN EQUINE ENCEPHALITIS DUE TO VACCINATION IN MAN. L. S. SUTTON and C. C. BROOKE, J. A. M. A. **155**:1473 (Aug. 21) 1954.

In 1949 a highly purified vaccine against Venezuelan equine encephalomyelitis for human use was developed. Inoculated volunteers showed excellent immunologic response. A review of the existing literature revealed that viremia had never been found after the administration of any of the three equine encephalomyelitis vaccines. The purpose of this paper is to report 14 cases of Venezuelan equine encephalomyelitis occurring in humans after inoculation with the vaccine. These 14 clinical cases were encountered in the immunization of 327 persons, who received a total of 1174 inoculations. All patients recovered.

Virus was isolated in specimens taken from 8 of 10 patients; no attempt at isolation was made in 4 cases. Although virus was recovered from only 8 of 10 persons, the authors note there is a good possibility that, had virus isolation studies been performed frequently and early enough, the agent would have been recovered from the other patients. None of the 14 persons were exposed to the virus during the course of their daily work. In seven of the eight cases virus was recovered from the blood. Viremia was detected as early as the first and as late as the fifth day of illness. The pharynx appears to be a site of predilection for this virus. Should virus not be isolated, presumptive diagnosis of the disease may be made by the demonstration of serum neutralizing antibodies. Although no attempt was made to recover the virus in the first four cases, the determination of neutralization indexes on postimmunization serums disclosed markedly elevated titers, which, coupled with the clinical illnesses, were suggestive of the disease. The clinical aspects of the disease occurring after vaccination are briefly reviewed and compared with naturally acquired cases.

Concentrated quantities of vaccine, including samples taken from the very vials containing vaccine causing clinical illnesses, were inoculated into about 6000 animals of various species. No virus was recovered. This may indicate that by chance a clump of injective particulate matter was injected into man, or that man may be a more susceptible host for the propagation and recovery of Venezuelan equine encephalomyelitis virus.

ALPERS, Philadelphia.

METASTATIC DYSGERMINOMA OF THE CENTRAL NERVOUS SYSTEM: A CASE REPORT WITH REVIEW OF THE LITERATURE. F. S. HADDAD and G. S. DUGGER, J. Neuropath. & Exper. Neurol. **13**:455 (July) 1954.

Dysgerminoma is an uncommon primary tumor of the ovary, arising from indifferent gonadic stem cells. Metastases to the central nervous system are extremely rare, and a third such case is

reported here. This was a 12-year-old girl who on first admission had signs of increased intracranial pressure, nystagmus, ataxia, and hypotonia of the left arm and leg. There was a left peripheral facial paralysis. At operation, a highly vascular tumor was seen arising from the region of the left foramen of Luschka. Microscopic diagnosis was medulloblastoma. Approximately two years after the intracranial surgery, a mass was palpated in the abdomen. Abdominal exploration revealed a solid tumor of the right ovary. Both tumors showed a similar microscopic picture. The diagnosis of dysgerminoma with intracranial metastases was then made.

SIEKERT, Rochester, Minn.

COMPARISON OF GENERAL PARESIS AND MULTIPLE SCLEROSIS IN REGARD TO THE ETIOLOGICAL AGENT. G. STEINER, J. Neuropath. & Exper. Neurol. **13**:492 (July) 1954.

Steiner believes that there is a close biologic relationship between the two microbial agents, Treponema pallidum in syphilis and Spirochaeta myelophthora in multiple sclerosis, and that this calls for a comparative study of these two diseases. He suggests that it also explains the many resemblances between late neurosyphilis and multiple sclerosis. A therapeutic postulate is suggested, namely, the treatment of multiple sclerosis with antibiotics.

SIEKERT, Rochester, Minn.

CEREBROSPINAL FLUID CHANGES FOLLOWING CLOSED CRANIOCEREBRAL INJURIES. R. A. DAVIS, Neurology **4**:422 (June) 1954.

The literature contains little material devoted specifically to the changes which are observed in cerebrospinal fluid determinations of the patient who has sustained a closed craniocerebral injury. Davis studied 43 such patients. They had no evidence of a fracture through the calvarium or the base of the skull on x-ray examination. There was a period of unconsciousness greater than five minutes; a diagnostic lumbar puncture was performed, with a careful manometric study and biochemical determinations, and a complete neurologic examination was performed for all patients under study. Lumbar punctures were done with the patient in the lateral position, and the cerebrospinal fluid was sent to the laboratory immediately for examination. In none of the patients did cerebrospinal fluid and blood escape from the nose, ears, or nasopharynx.

Davis found that in only six patients were the cerebrospinal fluid studies normal. The protein level was the most accurate cerebrospinal fluid guide to the severity of craniocerebral injury. The frequency of protein elevation generally varied directly with the length of unconsciousness. The level was increased in patients with permanent neurologic deficits and those who had neuropsychiatric disturbances.

When the determination was made within 90 hours after injury, the cerebrospinal fluid sugar value varied inversely to the period of unconsciousness and indicated the acuteness of the craniocerebral injury. The presence of more than 100 erythrocytes per cubic millimeter in the cerebrospinal fluid was not a reliable guide to the severity of the craniocerebral injury with absence of fracture through the calvarium. Protein elevations were usually independent of the elevated number of red cells in the cerebrospinal fluid.

There was no correlation between the state of consciousness and the intracranial pressure. However, most of the patients who had headaches following injury had an increased manometric reading. The chloride level of the cerebrospinal fluid was of little diagnostic importance in closed craniocerebral trauma, but did show a change following severe vomiting.

ALPERS, Philadelphia.

HOMONYMOUS HEMIANOPIA IN MULTIPLE SCLEROSIS. M. CHAMLIN and L. M. DAVIDOFF, Neurology **4**:429 (June) 1954.

Chamlin and Davidoff, in reviewing the literature, note that homonymous hemianopsia is a rare occurrence in multiple sclerosis. However, it may occur, and the authors present four such cases. Three of the four cases, as well as three found in the literature, showed dense paracentral components, suggesting that when the lesion of multiple sclerosis involves the posterior pathways, the site of involvement is apt to be near the occipital cortex. Three of these four cases showed spontaneous clearings of the field defects subsequently, while the fourth was seen only once.

ALPERS, Philadelphia.

CEREBELLAR SARCOMA WITH BONE METASTASES. W. H. KEHLER and E. BECK, Radiology **63**:736 (Nov.) 1954.

Kehler and Beck report the case of a patient who was found at autopsy to have a cerebellar sarcoma arising in the meninges and spreading along them and implanting itself on the dura covering the base of the skull. The patient was originally seen in June, 1948, when he had signs of increased intracranial pressure, moderate dilatation of the lateral and third ventricles, and clinical findings to suggest a tumor in the posterior fossa. A craniotomy was not successful in locating the tumor. Postoperative roentgen therapy produced rapid improvement. The patient was discharged asymptomatic after a tumor dose of 2300 r had been given to the posterior fossa in 18 days. From 1948 to 1951 the patient returned three times with serious recurrence of symptoms and each time was treated successfully by x-irradiation to the posterior fossa of the skull, with complete remission of symptoms. On the final admission, x-ray therapy was ineffective. At this time the patient had evidence of osteoblastic metastatic lesions in the lumbar spine, pelvis, thoracic spine, and ribs. He had evidence of depression of hematopoietic function.

Cerebellar sarcoma may mimic medulloblastoma both in its clinical symptoms and in the response to x-ray therapy. The presence of bone metastasis should make one consider the diagnosis of cerebellar sarcoma.

WEILAND, Grove City, Pa.

Diseases of the Spinal Cord

CERVICAL SPONDYLOSIS. RUSSELL BRAIN, Ann. Int. Med. **41**:439 (Sept.) 1954.

Cervical spondylosis is a degenerative disorder which is unrelated to inflammation and infection. The changes may involve the articulation between only one pair of vertebrae, or the lesions may be multiple. The main factor in the causation of cervical disc degeneration is age, and a large majority of patients are over the age of 50. Gradual degeneration of the disc occurs, and bony changes develop secondary to the disc degeneration. The great mobility of the cervical spine probably contributes to the wear and tear upon the discs, and a congenital abnormality or previous trauma may be a contributing factor.

Cervical spondylosis may cause damage to the spinal nerve roots or the spinal cord or both. The author discusses the role of compression, vascular changes, and obliteration of the root sleeve by fibrous tissue in affecting the nerve roots. He discusses the radicular symptoms, particularly symptoms of special interest, such as acroparesthesia, muscle wasting and weakness, and periarticular adhesions around the shoulder joint.

The effect of cervical spondylosis upon the spinal cord is produced by pressure, and probably vascular factors. Movements of the neck or a traumatic movement, especially forcible extension of the neck, may introduce a traumatic factor. The effect of these various factors is to produce in milder cases patches of demyelination with ascending and descending degeneration, while in severer cases, or after severe trauma, the result is an extensive necrosis of the cervical cord. The pathological changes may be called a myelomalacia. The clinical picture of such patients is extremely variable, depending on the level or levels of the lesion and the amount of damage to the cord. In the majority of cases the cerebrospinal fluid is normal in dynamics and composition.

In comparing the roentgenologic, operative, and pathologic findings, Brain stresses four general points: 1. Roentgenographic evidence of a narrowed intervertebral disc is not evidence of a disc protrusion. 2. Similarly, roentgenographic evidence of a narrowed intervertebral foramen is not evidence of compression of the corresponding nerve roots. 3. The presence of an intervertebral foramen which is normal roentgenographically is not evidence that the corresponding nerve roots are also normal, since they may be the site of root sleeve fibrosis. 4. Finally, cervical spondylosis is not necessarily the cause of associated symptoms of nervous disease, even when these are evidence of a lesion of the spinal cord in the cervical region.

In the natural course of the disease the lesion tends to progress slowly over several years and then to remain stationary, so that time is on the side of treatment.

The author believes that immobilization of the neck is the measure most likely to bring about arrest of the pathologic changes in the spinal cord. He is not impressed with the value of traction on the head, and believes that manipulation is a dangerous mode of treatment. In general, surgery is most likely to be successful when the patient is relatively young, when the

history is relatively short, when the disc protrusion is single rather than multiple, and when the cardiovascular system is normal. In surgery decompression is favored. When there is abnormal mobility of the intervertebral joints, fusion may be called for.

ALPERS, Philadelphia.

INTRAUTERINE POLIOMYELITIS INFECTION. M. SCHAEFFER, M. J. FOX and CHEN P. LI, J. A. M. A. **155**:248 (May 15) 1954.

The authors report a case which demonstrated poliomyelitis virus in both the placenta and the fetus infected during pregnancy.

The patient, a 24-year-old white woman, was admitted to hospital on the 11th day of illness, four days after weakness of her left arm was noted. The examination and laboratory findings are recorded. On the following day a spontaneous abortion occurred, with delivery of a macerated fetus. The mother's postabortive course was uneventful, and she was transferred a week later to another hospital for postpoliomyelitis treatment.

The placenta and fetus were refrigerated and sent for study to the virus laboratory. These studies were done two months later. Preparations from the fetus material was injected into a monkey, and fever developed on the fifth day and paralysis on the seventh. In the monkey receiving placenta material fever developed on the 10th day and paralysis on the 12th. Both animals showed typical poliomyelitis lesion on postmortem study. The virus isolated from both animals was identified as poliomyelitis virus Type 1.

ALPERS, Philadelphia.

ABSENCE OF TONSILS AS A FACTOR IN THE DEVELOPMENT OF BULBAR POLIOMYELITIS. G. W. ANDERSON and J. L. RONDEAU, J. A. M. A. **155**:1123 (July 24) 1945.

Recently the proportion of cases of poliomyelitis with bulbar paralysis has supposedly increased and is greater in the older age group. One of the factors that has been suggested as significant in this localization is whether or not tonsillectomy has been performed at any time previous to the illness. Anderson and Rondeau briefly review the findings of Top and Vaughan (1941) and four other studies, all of which indicate that the presence or absence of tonsils at the time of attack by the poliomyelitis virus appeared to be one of the factors determining the type of response to the virus invasion. The study reported here is an attempt to confirm the observations of Top and to explore some of the causative factors.

This investigation is based on epidemiological histories gathered during the 1946 outbreak in Minnesota. In all, 2669 histories were used in the study. The authors found that persons with the bulbar type of poliomyelitis give a history of removal of the tonsils more frequently than do persons with other forms of poliomyelitis and that, if clinically recognizable poliomyelitis develops in a person who has had his tonsils removed, the likelihood of bulbar involvement is four times as great as in one whose tonsils are in situ. This higher proportion of cases of bulbar involvement in patients who have had tonsillectomy occurs at all ages regardless of the time that has elapsed since operation. This higher proportion in older persons is due primarily to absence of the tonsils rather than to age per se. The higher proportion of bulbar involvement in recent years may be due to the greater frequency of tonsillectomy and the shift in age distribution of poliomyelitis to the ages at which tonsils may have been removed. The lack of cases of bulbar involvement in certain areas may be due to the concentration of poliomyelitis in ages before tonsil removal.

Numerous hypothesis that have been advanced to explain the above findings are discussed. It is pointed out that the excess of bulbar involvement in persons who have had tonsillectomy may possibly be due to direct invasion along fibers of the 9th and 10th cranial nerves.

The data here presented do not suggest that a child who has had a tonsillectomy is any more or less likely to have a recognizable form of the disease if he is infected. They do, however, show that if a recognizable form of the disease occurs in a person who has had tonsillectomy, it is more likely to be of the bulbar type than if the person had not had his tonsils removed. The authors draw no inference as to the desirability of tonsil removal but do suggest the importance of suitable indication for removal before operation is undertaken.

ALPERS, Philadelphia.

EPIDEMIOLOGICAL INVESTIGATIONS OF AMYOTROPHIC LATERAL SCLEROSIS. L. T. KURLAND and D. W. MULDER, Neurology **4**:355 (May); 438 (June) 1954.

The term "amyotrophic lateral sclerosis" as used in this study refers to the syndrome in which progressive muscular atrophy, progressive bulbar palsy, or progressive lateral sclerosis, alone or combined, occurs as the first symptom complex and usually progresses so that a combination of two or three of these symptom complexes are present in advanced stages of the disease. As a result of the observation of Arnold and associates, and of Koerna, that amyotrophic lateral sclerosis was highly prevalent on Guam, Kurland and Mulder carried out an epidemiological investigation in the Mariana and Caroline Islands. Forty-two patients were observed on Guam; 4 patients were found on Rota, and 1 patient was seen on Saipan.

On Guam, 120 case reports were collected, beginning with the period of Arnold's original observation in 1947. In all but one of these cases the patient was a Chamorro native; the exception was an atypical case of a Japanese who had resided on Guam for many years. No cases have been reported among the large number of Filipino laborers who are employed on Guam; there is no conclusive evidence to indicate that military personnel stationed on Guam have any greater risk of developing the disorder than those stationed elsewhere. Although the high prevalence of the disease may be due to a genetic trait, the existence of some exogenous etiological factor, unique to the Mariana Islands, was not ruled out.

Clinically, most of the patients observed had a typical form of amyotrophic lateral sclerosis, although two of the patients on Guam also had evidence of Parkinsonism. Clinical laboratory tests were principally of value in ruling out other conditions. Muscle biopsies showed chronic muscle atrophy. Necropsy specimens showed findings which were consistent with the diagnosis of amyotrophic lateral sclerosis.

On the basis of statistical studies made from many parts of the world, the geographic distribution, with the exception of the Mariana Islands, appears to be uniform and the disease relatively rare. On Guam and Rota, however, the prevalence ratio (about 200 per 100,000 population) is at least 50 times that of the rest of the world from which reports are available. On Guam, incidence of and mortality from amyotrophic lateral sclerosis are also about 50 times as high as reported elsewhere. As in the classic form of the disease, males are affected twice as often as females. Age distribution is similar to that of typical amyotrophic lateral sclerosis as reported by others. The mean age is 44 years; the range is 20 to 69 years.

On the basis of death certificates dating back to 1904, it appears that amyotrophic lateral sclerosis is not a new disease in Guam. This study suggests that the disease originated or has selectively persisted among the people of Umatac.

About 4% of all deaths and 8% to 10% of adult deaths on Guam are due to amyotrophic lateral sclerosis. The median survival period after onset for the entire group of patients was 3.0 years. There was no difference in these rates for the two sexes; patients in whom the disease developed at a younger age had a longer survival than those in whom it developed at older ages.

Kurland and Mulder's findings indicate that amyotrophic lateral sclerosis is highly endemic on Guam and Rota, and further study of this unusual situation is indicated.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

GUILLAIN-BARRÉ SYNDROME OCCURRING DURING CORTISONE THERAPY. H. GRANT and H. N. LEOPOLD, J. A. M. A. **155**:252 (May 15) 1954.

A 33-year-old white woman had been treated for severe rheumatoid arthritis for three years with cortisone and was on a usual maintenance dose of 100 mg. daily. One week before admission to hospital she developed gastrointestinal symptoms, accompanied by a low-grade fever, and three days later began having difficulty in walking, generalized weakness, and severe numbness involving both lower extremities and trunk. On the day of admission both legs were paralyzed and a paralysis of the left facial nerve had developed.

While neurologically the picture suggested hypopotassemia, an electrocardiogram was normal, and there was no benefit obtained by giving potassium chloride. Because of the flaccid paralysis with numbness, the preceding gastrointestinal disturbances, the facial paralysis, and the spinal fluid findings, a diagnosis of Guillain-Barré syndrome was made.

During the first week in hospital, the cortisone therapy was stopped with no apparent benefit and with actual progression of the disease. After the first week, because of increasing arthritic symptoms, cortisone therapy was resumed. After the second week, the patient began to show gradual but sustained improvement. Her deep reflexes returned, and the paralysis in the legs gradually disappeared. The facial paralysis had gone except for slight residual weakness.

The authors suggest that the cortisone had no direct causative bearing on the development of the Guillain-Barré syndrome in this case.

ALPERS, Philadelphia.

SYSTEMIC DISEASE AND THE CARPAL TUNNEL SYNDROME. A. W. GROKOEST and F. E. DEMARTINI, J. A. M. A. **155**:635 (June 12) 1954.

Median nerve compression in the volar carpal tunnel (the carpal tunnel syndrome) has been recognized as an effect of trauma, and has been ascribed in other reports to the tenosynovitis of rheumatoid arthritis. In this report the authors call attention to the importance of underlying disorders that, in the absence of trauma, may lead to the carpal tunnel syndrome.

The authors describe three patients with the syndrome associated with a systemic disease who came to operation. One had multiple myeloma with amyloid disease; another had primary amyloid disease, and a third had rheumatoid arthritis.

Besides the patient operated on, plasma cell myeloma with amyloid disease and median neuritis were observed in three other patients on whom exploration of the carpal tunnel was not done.

The pertinent clinical findings for these four cases were as follows: The illness began with a median neuritis, which became bilateral in a short time. Diffuse swelling of the first three fingers and a variety of flexion contractures developed. Subcutaneous nodes obviously attached to tendon sheaths were confused with signs of rheumatoid arthritis. A heavy proteinuria was present: The conventional test for Bence Jones protein was positive in two cases. There was no hyperglobulinemia: The highest figure was 2.2 gm. per 100 cc. Myeloma cells were found in the bone marow of all these patients, and biopsy specimens of tendon sheaths in three instances and tongue nodules in one showed amyloid.

In the experience of these workers the carpal syndrome occurs in rheumatoid arthritis but its incidence is low.

The treatment of the carpal tunnel syndrome is primarily that of decompression. It would seem advisable, on the basis of findings in patients in this report, to perform a biopsy on the tissues responsible for the median nerve compression. Special histological techniques for the demonstration of amyloid are important.

ALPERS, Philadelphia.

POLYNEURITIS AND RADICULITIS ASSOCIATED WITH MULTIPLE MYELOMA. H. R. ESTES and C. H. MILLIKAN, Proc. Staff Meet., Mayo Clin. **29**:453 (Aug. 11) 1954.

It has been recognized that multiple myeloma may involve the nervous system. This involvement is usually on the basis of compression of the spinal cord by a tumor mass, collapsed vertebrae, or other mechanical involvement of nerve structures. However, multiple myeloma may be associated with neurologic changes other than those associated with compression of nerve tissue. Estes and Millikan describe such a patient, a woman of 43, whose presenting symptoms were those of polyneuritis and radiculitis and who was found to have multiple myeloma. Apparently the neurologic abnormality was secondary to the myeloma. There was no evidence of direct involvement of nerve structures by tumor or bone collapse. It is suggested that perhaps some toxic factor was operative.

ALPERS, Philadelphia.

Treatment, Neurosurgery

REVASCULARIZATION OF THE BRAIN IN MENTAL DEFECTIVES. G. A. JERVIS, F. F. MCALLISTER, B. M. HOGG, and R. A. DETERLING, Neurology **3**:871 (Dec.) 1953.

In 1949, Beck, McKhann, and Belnap introduced a new operative procedure designed to increase the arterial blood supply to the cerebral cortex by establishing an arteriovenous anastomosis between the carotid artery and the internal jugular vein. It was claimed that the operative procedure produces beneficial effects in patients in whom the function of cortical cells has been rendered abnormal, but not entirely suppressed, through past injury.

Results on the effects of the Beck-McKhann procedure have been reported in a total of 331 cases. The results of the operation thus far reported differ considerably. Data obtained by other investigators are summarized.

Jervis and his colleagues carried out this operative procedure aimed at revascularization of the brain on 25 mentally defective children. In 10 children the mental defect was postencephalitic; in 7, post-traumatic in origin; 7 children were epileptic defectives, and 1 suffered from childhood schizophrenia. The period of postoperative observation extended to two years or more.

These investigators observed no significant improvement in intelligence quotients, clinical symptomatology, or electroencephalographic findings. Some theoretical aspects of the operative procedure are briefly discussed.

ALPERS, Philadelphia.

MULTIPLE OPERATIONS FOR PROTRUDED LUMBAR INTERVERTEBRAL DISK. J. H. KELLEY, D. C. VORIS, H. J. SVIEN, and R. K. GHORMLEY, Proc. Staff Meet., Mayo Clin. **29**:546 (Sept. 29) 1954.

The results of treatment in a group of 54 patients who had two unsuccessful operations for protruded lumbar intervertebral disk were studied. In the care of these patients subsequent to the two unsuccessful operations, 27 were treated by conservative measures, while the other 27 underwent a third operation.

Conservative treatment consisted of adequate back support, use of a firm mattress, physical therapy, and limitation of certain activities. Acceptable improvement was obtained in 14 of the 27 patients treated conservatively, and no improvement occurred in the remaining 13 so treated.

Of the 27 patients who underwent a third operation, 15 had protruded disks which were removed. In these 15 patients, 16 fusions were performed, with the following results: good, 6 cases; fair, 5 cases, and poor, 5 cases. In the other 12 patients treated surgically no protruded disks were found, but in some cases adhesions surrounding the nerve roots were noted. In general those cases in which a protruded disk was found at the third operation had better results than in the second group of cases.

In reviewing these results, it was noted that of the 15 patients who underwent a third operation in which a disk was found, 9 showed the protrusion at the level at which the first or second previous operation had been performed. This would indicate that the surgeon should not be content to remove just the protruded portion of the intervertebral disk, but should attempt to evacuate the disk space as completely as possible. In 4 of these 15 cases a protruded disk was found at a different level from the one at which such a disk was removed initially. This observation suggests the necessity of carrying out myelography, not only initially, but before each operation.

In the cases in which no protruded disk is found at the third operation, other causes of pain must be invoked. Such causes may be nerve root adhesions or skeletal changes or instability. The problem of the various intraspinal contrast media used in myelography as possible irritative factors needs further study. Psychoneurosis, addiction to narcotics, and the element of compensation all may play a role in the failures.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

THE SIZE OF THE SELLA TURCICA BY AGE AND SEX. L. L. HAAS, Am. J. Roentgenol. **72**:754 (Nov.) 1954.

Haas describes modifications of his method of measuring the sella turcica which have been necessitated by advances in roentgenological equipment and technique and reports a study of sellar size in a group of children and adults of both the white and the Negro race in Illinois. Lateral roentgenograms of the skull are used for measurement of the sellar size, and the area of the sella turcica, in square millimeters, is calculated from these films. Haas uses a 36-in. (91 cm.) target-film distance and a Bucky grid. The distance from the film to the surface of the x-ray table is 5.6 mm. The distance of the sella turcica to the table top in all subjects except those with swellings or deformities of the skull is constant enough that the variation in distance can be ignored.

The mean value for the area of adult male sella turcicas was 86.1 sq. mm., and for adult females it was 87.2 sq. mm. For practical purposes the values of 58 and 120 sq. mm. can be regarded as the limits of normal sellar areas in adults. The subjective estimation by eye of sella size is sufficient for clinical purposes if the sella is of average shape and size and the

interpreter has some experience in skull roentgenography. The measurement of area is essential in academic investigations and is useful in borderline cases to follow small changes in size in any one patient and when the profile of the sella is obscured by confusing contours.

Haas discusses the information obtained from and limitations of the use of the method of measurement of sellar area. There is some parallelism between the size of the pituitary gland and that of the pituitary fossa, but this parallelism is not absolute or constant. The factors which cause this discrepancy between the two sizes must be understood by those interpreting the roentgenograms. A normal-sized pituitary fossa can contain an abnormal gland. However, almost all patients whose sella turcica measures larger than the normal limits have some abnormality to cause this enlargement. An abnormal sellar size usually has definite clinical significance.

WEILAND, Grove City, Pa.

CEREBRAL ANGIOGRAPHY IN CAROTID CAVERNOUS COMMUNICATIONS. T. C. PARSONS, H. G. WOLFF, E. J. GULLER, and H. S. DUNBAR, Neurology **4**:65 (Jan.) 1954.

Caroticocavernous fistulae are frequently post-traumatic, although about 25% of cases appear to be spontaneous, with no specific traumatic antecedent. Traumatic caroticocavernous fistulae are usually secondary to basal skull fractures consequent to the application of force either to the anterior or to the lateral aspect of the head.

In the case reported here, the patient had two generalized grand mal type seizures, and as a result of the second seizure she fell, striking the occiput. A skull x-ray disclosed no fractures. From examination and study of the patient a diagnosis of arteriovenous carotid-cavernous fistula was made.

A spontaneous occlusion occurred following angiography. Angiograms before and after closure of the communication are shown. The authors infer that the locally irritating and vasoconstrictive effect of the radiopaque medium utilized in the performance of angiography contributed toward thrombosis of the fistula.

ALPERS, Philadelphia.

THE "FALSE POSITIVE" LUMBAR MYELOGRAM. W. V. TROWBRIDGE and J. D. FRENCH, Neurology **4**:339 (May) 1954.

In recent years the accuracy of the myelogram in cases with lumbar disk lesions has been found to be far from perfect. "False-negative" findings have commonly been considered to constitute the largest source of error in lumbar myelography. Similarly, "false-positive" myelograms have been described, their incidence varying between 3.5% and 5.3% in different series.

In a period of two years all persons studied with cervical myelography by the authors were carefully questioned concerning previous difficulties referrable to the lumbar spinal region. From this entire group, 25 persons were found who denied any history of low back pain, sciatica, or other evidences of lumbar nerve root or cauda equina compression. Routine lumbar myelography was done in this group of 25 patients, using the standard technique for cervical myelography.

A total of 14 abnormal lumbar myelograms were obtained in this regionally asymptomatic group, constituting 56% of the total cases studied. These findings suggest that "false-positive" myelograms are probably not as uncommon as was previously thought.

The authors point out that the presence of a defect in the lumbar myelogram does not necessarily indicate the site of a symptomatic lesion. Also, the presence of a lumbar myelographic defect constitutes no assurance that conservative therapy will be unsuccessful. Although it continues to be a useful adjunct to clinical evaluation, they feel the lumbar myelogram should not be used in questionable cases or to establish the presence of an abnormality for medicolegal purposes. The myelogram should be reserved for the study of those cases in which surgery is contemplated, and even then it should be subjected to a critical evaluation in the light of clinical findings.

ALPERS, Philadelphia.

ARTERIOGRAPHIC DEMONSTRATION OF EXTERNAL-INTERNAL CAROTID ANASTOMOSIS THROUGH THE OPHTHALMIC ARTERIES. J. M. TAVERAS, L. A. MOUNT, and R. M. FRIENDENBERG, Radiology **63**:525 (Oct.) 1954.

Small anastomotic branches exist between the external and the internal carotid arteries. All of these anastomoses occur in branches of the ophthalmic arteries. Normally these anasto-

moses are small and contribute very little to the circulation of the brain. Ligation or obstruction of the internal carotid artery on one side causes enlargement of the anastomoses, and the brain receives a significant amount of its blood supply through the ophthalmic artery from the external carotid artery.

Taveras, Mount, and Friendenberg report four clinical case histories to illustrate the importance of this anastomosis. In three patients the internal carotid arteries had been ligated surgically because of aneurysms in the region of the carotid siphon. The cerebral angiograms were repeated several months after ligation. In all cases the carotid artery was injected proximal to the site of ligation. No filling of the internal carotid was obtained in the neck above the site of ligation. Filling of the external carotid artery was obtained; the ophthalmic artery was visualized, and varying degrees of filling of the carotid siphon and middle meningeal artery were obtained. The fourth case is that of a patient presumed to have thrombosis of the internal carotid artery. This patient was thought to have an aneurysm of the carotid artery in the region of the siphon. Cerebral angiograms failed to visualize the cervical portion of the internal carotid artery. Despite the fact that the injection was made into the internal carotid artery, the external carotid artery, the ophthalmic artery, the carotid spihon, and the middle cerebral artery were filled.

The authors feel that serialograms are necessary for the study for the collateral circulation, since the blood flow is slower through the collateral channels than through the internal carotid system. In their cases no compression of the opposite carotid artery was made while the serialograms were taken. Since they wrote their article they have seen five additional cases of spontaneous thrombosis of the internal carotid artery in the neck which showed retrograde flow through the ophthalmic artery. Two of 10 cases of postligation angiography have showed retrograde flow through the ophthalmic artery.

WEILAND, Grove City, Pa.

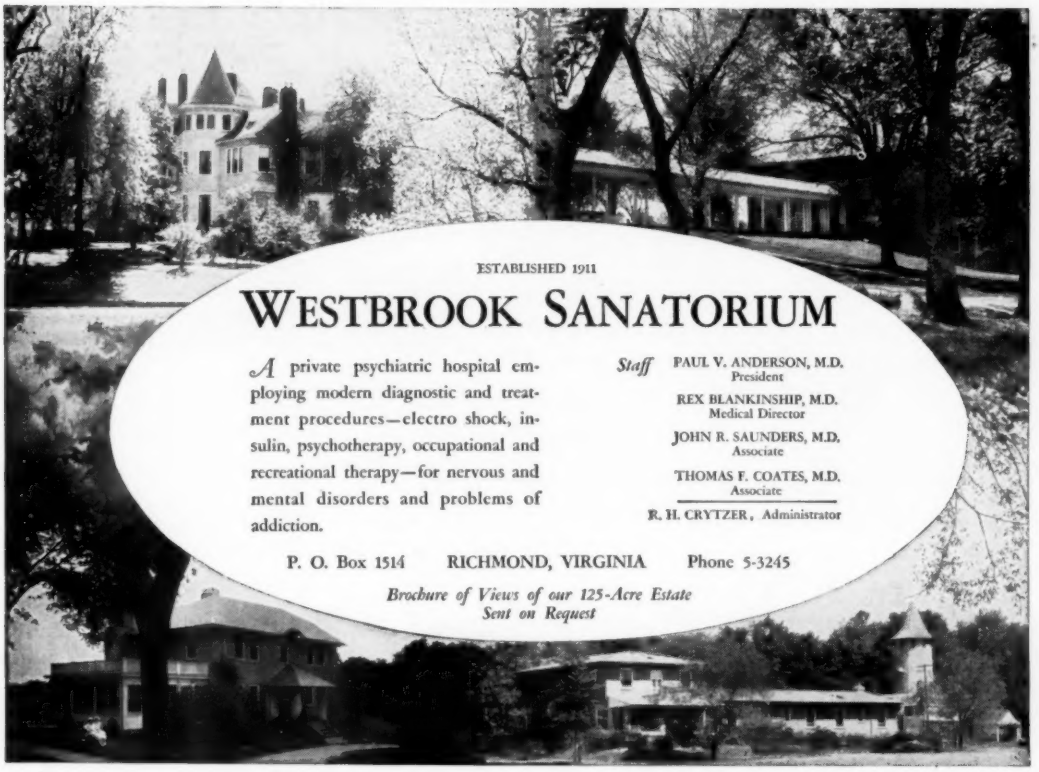
PANEL DISCUSSION ON LOW-BACK PAIN. J. R. WINSTON, R. D. MORETON, D. E. BIBBY, C. WILLIAMS, C. L. EWING, R. M. POTTER, and J. R. NORCROSS, Radiology **63**:664 (Nov.) 1954.

The panel discussion on low back pain concerned itself mainly with a discussion of the use of preemployment roentgenograms of the lumbar spine and the incidence of spondylolithesis and defects in the neural arch in such roentgenograms. Four thousand consecutive examinations of the low back were performed on applicants for employment by the Santa Fe Railroad, and the participants in the discussion all had some responsibility concerning the medical and legal problems arising from these examinations. Winston and Moreton reported that they had devised a survey examination of the lumbar spine which consisted of anteroposterior, lateral, and both oblique films.

Moreton, Bibby, Winston, and Williams reported that the incidence of spondylolithesis in their series of 4000 cases was 4%. All cases of spondylolisthesis involved one of the two lowest lumbar vertebrae, and 97% of them involved the lowest lumbar vertebra. The method of Garland was used to determine whether or not spondylolisthesis was present. One draws a line along the superior surface of the vertebral body below the suspected vertebra. A perpendicular to this line is erected exactly at the anterior superior edge of the body below the suspected vertebra. If the suspected vertebra touches or overlaps this perpendicular line, spondylolisthesis is present. Although 160 patients were found with spondylolisthesis, 272 isthmus defects were found in the 4000 cases surveyed. Most of the isthmus defects were bilateral and affected the last lumbar vertebra.

Potter and Norcross discussed the finding of spondylolisthesis without a demonstrable isthmus defect. Spondylolisthesis may result from arthritic erosion of the zygapophyseal joints without an isthmus defect. In such cases the spinous process of the involved segment moves forward along with the body. The changes in the zygapophyseal joints can readily be demonstrated in roentgenograms of the spine.

WEILAND, Grove City, Pa.



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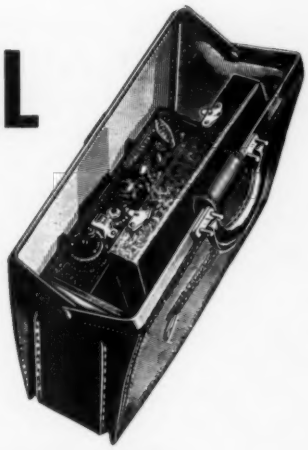

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